



Australian Government

PCT/JP 2004/005987

25.05.2004

Patent Office
Canberra

REC'D 17 JUN 2004

WIPO

PCT

I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003903861 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 24 July 2003.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

WITNESS my hand this
Twenty-ninth day of April 2004

JULIE BILLINGSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

BEST AVAILABLE COPY



Fujisawa Pharmaceutical Co., Ltd.

A U S T R A L I A

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Inhibitor of cox"

The invention is described in the following statement:

DESCRIPTION

INHIBITOR OF COX

5 TECHNICAL FIELD

This invention relates to imidazole compounds and pharmaceutically acceptable salts thereof having pharmacological activity.

Moreover, this invention relates to medicament or pharmaceutical composition comprising the above mentioned imidazole compounds or
10 pharmaceutically acceptable salts thereof as an active ingredient.

BACKGROUND ART

Some imidazole derivatives having anti-inflammatory and/or analgesic activities have been known, for example, WO 96/03388. However,
15 all of compounds disclosed in this document are substituted by sulfonyl group on imidazole ring. And the compounds disclosed in WO 96/03388 selectively inhibit cyclooxygenase-II (COX-II) over cyclooxygenase-I (COX-I).

20 DISCLOSURE OF THE INVENTION

As a result of studies on the synthesis of imidazole compounds and their pharmacological activity, the inventors of this invention have found that the imidazole compounds of this invention have superior activity of inhibiting COX (especially, COX-I inhibiting activity).
25 So, this invention relates to imidazole compounds, which have pharmaceutical activity such as COX inhibiting activity, to a medicament and a pharmaceutical composition containing the imidazole compounds.

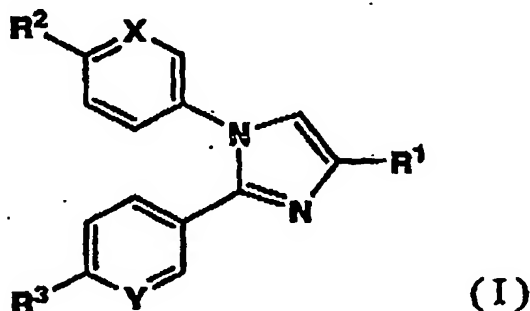
Accordingly, one object of this invention is to provide the imidazole compounds, which have a COX inhibiting activity.

30 Another object of this invention is to provide a method for treatment and/or prevention and the imidazole compounds for use in the treatment and/or prevention of the disease associated with COX.

A further object of this invention is to provide a use of the imidazole compounds for manufacturing a medicament for treating or preventing the diseases and the analgesic agent comprising the imidazole compounds which is usable for treating and/or preventing pains.

5

The imidazole compounds of this invention can be represented by the following general formula (I):



10

{wherein

R¹ is (lower)alkyl, halogen-substituted (lower)alkyl, hydroxy-substituted (lower)alkyl, cycloalkyl, carbamoyl, N-[(lower)alkyl]carbamoyl, N,N-di[(lower)alkyl]carbamoyl, formyl, (lower)alkanoyl, carboxy, [(lower)alkoxy]carbonyl, cyano, cycloalkylcarbonyl or heterocycliccarbonyl;

15

R² is halogen, cyano, hydroxy, (lower)alkoxy, aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl, carbamoyl, formyloxy, (lower)alkanoyloxy, [(lower)alkyl]sulfonyloxy, [halogen-substituted (lower)alkyl]sulfonyloxy or carboxy;

20

R³ is (lower)alkoxy, hydroxy, amino, [(lower)alkyl]amino, or di[(lower)alkyl]amino;

X and Y are each CH or N]

25

or pharmaceutically acceptable salts thereof.

In the above and subsequent description of the present specification,

suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

5 So, the "(lower)alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, or the like, and it is preferably (C1-C4)alkyl, more preferably (C1-C2)alkyl, most preferably methyl.

10 The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, and is preferably a fluorine atom or a chlorine atom, more preferably a fluorine atom.

15 The "halogen-substituted (lower)alkyl" means a monovalent group in which the above lower alkyl is substituted by the above halogen atom(s), such as fluoromethyl, chloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, or the like, and it is preferably halogen-substituted (C1-C4)alkyl, more preferably halogen-substituted (C1-C2)alkyl, more preferably
20 fluorine-substituted (C1-C2)alkyl, more preferably fluorine-substituted methyl, most preferably difluoromethyl or trifluoromethyl.

25 The "hydroxy-substituted (lower)alkyl" means a monovalent group in which the above (lower)alkyl is substituted by a OH group, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 1-hydroxyisopropyl, 2-hydroxyisopropyl, hydroxybutyl, hydroxyisobutyl, hydroxy-tert-butyl, hydroxyhexyl, or the like, and it is preferably hydroxy-substituted (C1-C4)alkyl, more preferably hydroxy-substituted (C1-C2)alkyl, most preferably hydroxymethyl.

30 The "cycloalkyl" means (C3-C10)cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, or the like, and it is preferably

(C3-C6)cycloalkyl, more preferably (C3-C5)cycloalkyl, most preferably cyclopropyl.

5 The "N-[(lower)alkyl]carbamoyl" means a carbamoyl group substituted by the above (lower)alkyl group on nitrogen atom, such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, tert-butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, or the like, and it is preferably N-[(C1-C4)alkyl]carbamoyl, more preferably N-[(C1-C2)alkyl]carbamoyl.

10 The "N,N-di[(lower)alkyl]carbamoyl" means a carbamoyl group substituted by the same or different above two (lower)alkyl groups on nitrogen atom, such as dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, diisobutylcarbamoyl, dipentylcarbamoyl, dihexylcarbamoyl, 15 ethylmethylcarbamoyl, methylpropylcarbamoyl, butylmethylcarbamoyl, ethylpropylcarbamoyl, butylethylcarbamoyl, or the like, and it is preferably di[(C1-C4)alkyl]carbamoyl, more preferably di[(C1-C2)alkyl]carbamoyl.

20 The "(lower)alkanoyl" means carbonyl group which is substituted by the above (lower)alkyl groups, such as acetyl, propionyl (ethylcarbonyl), butyryl, isobutyryl (isopropylcarbonyl), pivaloyl, valeryl, isovaleryl, hexanoyl, and the like, and it is preferably (C2-C5)alkanoyl, more preferably (C2-C4)alkanoyl.

25 So, "(lower)alkanoyloxy" may be exemplified by acetyloxy, propionyloxy (ethylcarbonyloxy), butyryloxy, isobutyryloxy (isopropylcarbonyloxy), pivaloyloxy, valeryoxyl, isovaleryloxy, hexanoyloxy, and the like, and it is preferably (C2-C5)alkanoyloxy, more preferably (C2-C4)alkanoyloxy.

30 The "(lower)alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, and it is preferably (C1-C4)alkoxy, more preferably (C1-C2)alkoxy, most

preferably methoxy.

The "cycloalkylcarbonyl" means carbonyl group substituted by the above cycloalkyl group, such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, norbornylcarbonyl, adamantylcarbonyl, or the like, and it is preferably [(C3-C6)cycloalkyl]carbonyl, more preferably [(C3-C5)cycloalkyl]carbonyl.

The "heterocycle" means 5- or 6-membered saturated heterocyclic group which contains at least one hetero atom such as nitrogen, oxygen, sulfur atom. The "heterocycle" may include 5-membered heterocyclic group such as pyrrolidinyl, imidazolidinyl, pyrazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, or the like; and 6-membered heterocyclic group such as piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or the like.

So, the "heterocycliccarbonyl" may be exemplified pyrrolidinylcarbonyl, imidazolidinylcarbonyl, pyrazolidinylcarbonyl, tetrahydrothiophenylcarbonyl, tetrahydrofuranylcarbonyl, oxazolidinylcarbonyl, isoxazolidinylcarbonyl, thiazolidinylcarbonyl as 5-membered heterocycliccarbonyl group; and piperidinylcarbonyl, piperazinylcarbonyl, morpholinylcarbonyl, thiomorpholinylcarbonyl as 6-membered heterocycliccarbonyl group. And it is preferably (heterocyclic containing nitrogen atom)carbonyl or 6-membered heterocycliccarbonyl, more preferably piperidinylcarbonyl.

The "aryl[(lower)alkyl]oxy," means the above mentioned (lower)alkoxy group which is substituted with aryl group, such as benzyloxy, nephtylmethyloxy, indenylmethyloxy, phenetyl, nephtylethyl, phenylpropyl, phenylbutyl, phenylhexyl, or the like, and it is preferably aryl[(C1-C2)alkyl]oxy, more preferably arylmethoxy, most preferably benzyloxy.

The "[(lower)alkoxy]carbonyl" means a -CO₂-[(lower)alkyl] group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,

isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, and the like, and it is preferably [(C1-C4)alkoxy]carbonyl, more preferably ethoxycarbonyl.

5 The "[(lower)alkyl]sulfonyl" means a sulfonyl group substituted with (lower)alkyl group mentioned above, such as methanesulfonyl, ethanesulfonyl, isopropanesulfonyl, tert-butanesulfonyl, and the like, and it is preferably (C1-C4)alkanesulfonyl, more preferably (C1-C2)alkanesulfonyl, most preferably methanesulfonyl.

10 So, "[(lower)alkyl]sulfonyloxy" may be exemplified by methanesulfonyloxy, ethanesulfonyloxy, isopropanesulfonyloxy, tert-butanesulfonyloxy, and the like, and it is preferably (C1-C4)alkanesulfonyloxy, more preferably (C1-C2)alkanesulfonyloxy, most preferably methanesulfonyloxy.

15 The "[halogen-substituted (lower)alkyl]sulfonyl" means a sulfonyl group substituted with halogen-substituted (lower)alkyl mentioned above, such as trifluoromethanesulfonyl, and the like, and it is preferably halogen-substituted (C1-C4)alkylsulfonyl, more preferably halogen-substituted (C1-C2)alkylsulfonyl, most preferably
20 trifluoromethanesulfonyl.

So, "[halogen-substituted (lower)alkyl]sulfonyloxy" may be exemplified by trifluoromethanesulfonyloxy, and the like, and it is preferably halogen-substituted (C1-C4)alkanesulfonyloxy, more preferably halogen-substituted (C1-C2)alkanesulfonyloxy, most
25 preferably trifluoromethanesulfonyloxy.

The "[(lower)alkyl]amino" means a amino group substituted by the above lower alkyl group, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, pentylamino, hexylamino, or the like, and it is preferably
30 [(C1-C4)alkyl]amino, more preferably [(C1-C2)alkyl]amino.

The "di[(lower)alkyl]amino" means a amino group substituted by the same or different above (lower)alkyl groups, such as dimethylamino,

diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, dipentylamino, dihexylamino, ethylmethylanino, methylpropylamino, butylmethylanino, ethylpropylamino, butylethylanino, or the like, and it is preferably di[(C1-C4)alkyl]amino, more preferably di[(C1-C2)alkyl]amino.

The combination of X and Y is X and Y are each CH, X is N and Y is CH, X is CH and Y is N, X and Y are each N, preferably X and Y are each CH, X is N and Y is CH, or X is CH and Y is N, and any of these three combination are preferable.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The imidazole compounds of this invention can be converted to salt according to a conventional method. Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g.,

hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

5 The imidazole compound (I) may preferably include wherein

R^1 is (lower)alkyl, halogen-substituted (lower)alkyl, cycloalkyl, N,N-di[(lower)alkyl]carbamoyl, (lower)alkanoyl, or cyano;

R^2 is halogen, cyano, hydroxy, or lower alkoxy;

10 R^3 is lower alkoxy;

X and Y are each CH, X is N and Y is CH, or X is CH and Y is N.

And in the each definition of the compound formula(I), preferably,

15 (1) R^1 is (lower)alkyl, halogen-substituted (lower)alkyl, cycloalkyl, carbamoyl, N,N-di[(lower)alkyl]carbamoyl, (lower)alkanoyl or cyano,

(2) R^1 is (lower)alkyl, halogen-substituted (lower)alkyl, cycloalkyl,

(3) R^1 is (C1-C4)alkyl, halogen-substituted (C1-C4)alkyl or (C3-C6)cycloalkyl,

20 (4) R^1 is (C1-C2)alkyl, halogen-substituted (C1-C2)alkyl or (C3-C5)cycloalkyl,

(5) R^1 is carbamoyl or N,N-di[(C1-C4)alkyl]carbamoyl,

(6) R^1 is carbamoyl or N,N-di[(C1-C2)alkyl]carbamoyl,

(7) R^1 is (C2-C4)alkanoyl or cyano,

25 (8) R^2 is halogen, cyano, hydroxy, (lower)alkoxy,

aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl, carbamoyl or [halogen-substituted (lower)alkyl]sulfonyloxy,

(9) R^2 is halogen, cyano, hydroxy, (C1-C4)alkoxy, arylmethoxy, [(C1-C4)alkoxy]carbonyl, carbamoyl or [halogen-substituted

30 (C1-C4)alkyl]sulfonyloxy,

(10) R^2 is halogen, cyano, hydroxy or (C1-C2)alkoxy,

(11) R^2 is hydroxy or (C1-C2)alkoxy.

(12) R³ is (lower)alkoxy or hydroxy,

(13) R³ is (C1-C4)alkoxy,

(14) R³ is (C1-C2)alkoxy.

(15) X and Y are each CH.

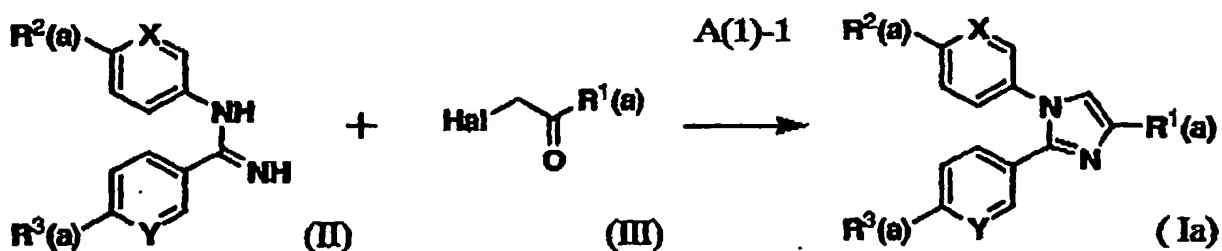
5 (16) X is N and Y is CH.

(17) X is CH and Y is N.

(18) X and Y are each N.

10 The compound of the formula (I) of the present invention can be prepared according to the following process.

Process A(1)



15 In the above formulae, X and Y represent the same meanings as defined above. R¹(a), R²(a) and R³(a) represent the group in the definition of R¹, R² and R³, respectively, which do not influence this process. Concretely, R¹(a) represents (lower)alkyl, halogen-substituted (lower)alkyl, cycloalkyl, N,N-di[(lower)alkyl]carbamoyl, formyl, (lower)alkanoyl, [(lower)alkoxy]carbonyl, cyano or
20 cycloalkylcarbonyl; R²(a) represents halogen, cyano, (lower)alkoxy, aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl, formyloxy, (lower)alkanoyloxy, [(lower)alkyl]sulfonyloxy or [halogen-substituted (lower)alkyl]sulfonyloxy; R³(a) represents is
25 lower alkoxy. "Hal" represents halogen atom, especially, chlorine or bromine atom.

Process A(1) is the process for preparing the compound (Ia), which corresponds to compound (I) in which R¹ to R³ are not reactive groups.

This process is carried out by reacting compound (II) and compound (III) in the presence of base to form imidazole ring.

Compound (II) may be purchased if it is commercial, or synthesized according to Processes B mentioned after or other general methods from commercial compounds. Compound (III) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds, because compound (III) as starting compound for synthesis of compound (Ia) have comparatively simple structure.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as methanol, ethanol, 2-propanol; ethers such as diisopropyl ether, tetrahydrofuran, dioxane; and mixed solvent of these.

The base employable in this process for making basic condition is not particularly limited so long as it accelerate this reaction and may include alkali metal hydrogencarbonates such as lithium hydrogencarbonate, sodium hydrogencarbonate and potassium hydrogencarbonate; alkali metal carbonates such as lithium carbonate, sodium carbonate and potassium carbonate; alkaline earth metal carbonates such as magnesium carbonate and calcium carbonate; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide, preferably alkali metal hydrogencarbonates, especially sodium hydrogencarbonate.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50°C to 150°C, preferably from 60°C to 100°C or reflux condition.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1hr to 1day, preferably from 2hrs to 12hrs.

After the reaction, the reaction mixture is cooled to room temperature and evaporated in vacuo, then added water and extracted with organic solvent immiscible with water such as ethyl acetate. The organic layer is washed with water or the like, dried over anhydrous

magnesium sulfate or sodium sulfate, evaporated in vacuo, and the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc.

5 According to the starting material, the heterocyclic ring is formed but not to form imidazole ring. In such case, the dehydration process is needed to form imidazole ring.

The dehydration process is carried out in the hot and acidic condition.

10 The solvent employable in this process is not particularly limited, but acid such as acetic acid, sulfuric acid or the like may be used as solvent.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50°C to 200°C, preferably from 80°C to 150°C.

15 The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 30min to 5hrs, preferably from 1hr to 3hrs.

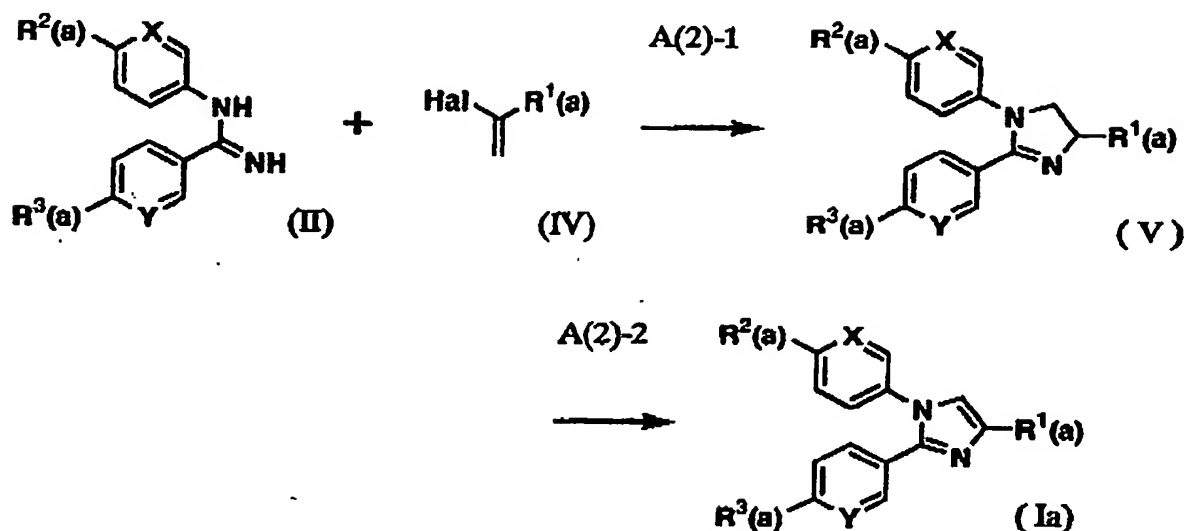
20 After the reaction, the mixture is poured into basic water, and extracted with organic solvent insoluble with water such as ethyl acetate. The organic layer is washed with water or the like, dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo, and the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc.

25

30

Compound (Ia) can also be synthesized according to the following process.

Process A(2)



5

In the above formulae, $R^1(a)$, $R^2(a)$, $R^3(a)$, X, Y and Hal represent the same meanings as defined above.

Process A(2) is the process for preparing the compound (Ia), which corresponds to compound (I) in which R^1 to R^3 are not reactive groups.

In this process, first, compound (II) is condensed to compound (IV) for synthesis of compound (V) (Process A(2)-1).

Process A(2)-1 is carried out under in the presence of Hunig's base (N,N-diisopropylethylamine).

Compound (IV) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds, because compound (IV) have comparatively simple structure.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diisopropyl ether, tetrahydrofuran, dioxane, preferably tetrahydrofuran.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50°C to 200°C, preferably

from 50°C to 120°C or reflux condition.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1hr to 2days, preferably 1hr to 5hrs or over night.

5 If the reaction does not proceed adequately, additional compound (IV) may be added.

After the reaction, the desired compound (V) is collected from the reaction mixture according to a conventional method. For example, after cooled to room temperature and evaporated in vacuo, the reaction
10 mixture is poured into water and extracted with organic solvent immiscible with water such as ethyl acetate. The organic solvent is washed with water or the like, dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo, and the desired compound is purified by the conventional method such as silica gel column
15 chromatography, recrystallization, etc.

Process A(2)-2 is the oxidation process to form imidazole ring in the presence of catalyst.

The oxidative catalyst employable in this process is not particularly limited so long as it can catalyze the reaction from
20 4,5-dihydro-imidazole derivative (V) to imidazole derivative and may include manganese(IV) oxide (MnO_2).

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include amides such as N,N-dimethylformamide, dimethylacetamide, hexamethylphosphoric
25 triamide; aromatic hydrocarbon such as benzene, toluene; or the like.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50°C to 200°C, preferably from 80°C to 120°C or reflux condition.

The reaction time varies depending on the starting material, the
30 solvent, the reaction temperature, etc., but it is usually from 1hr to 24hrs, preferably 2hrs to 12hrs.

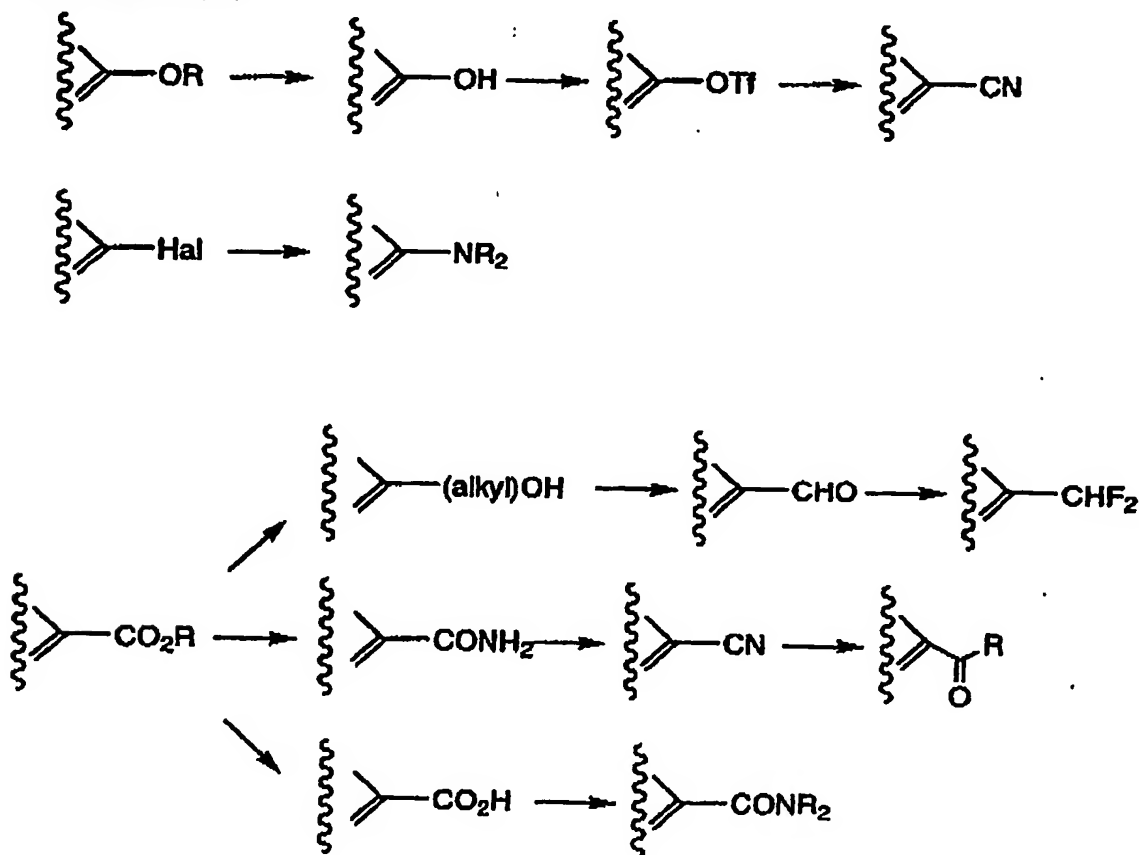
If the reaction does not proceed adequately, additional catalyst

may be added.

After the reaction, the mixture is cooled to room temperature and filtered to remove catalyst. The organic fraction is concentrated in vacuo, or poured into basic water, and extracted with organic solvent insoluble with water such as ethyl acetate. The organic layer is washed with water or the like, dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo. The desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc.

Compound (Ia) can be transformed into compound (I) by functional group transformation, which is obvious to the person skilled in the organic chemistry. For example, such reactions are illustrated as following.

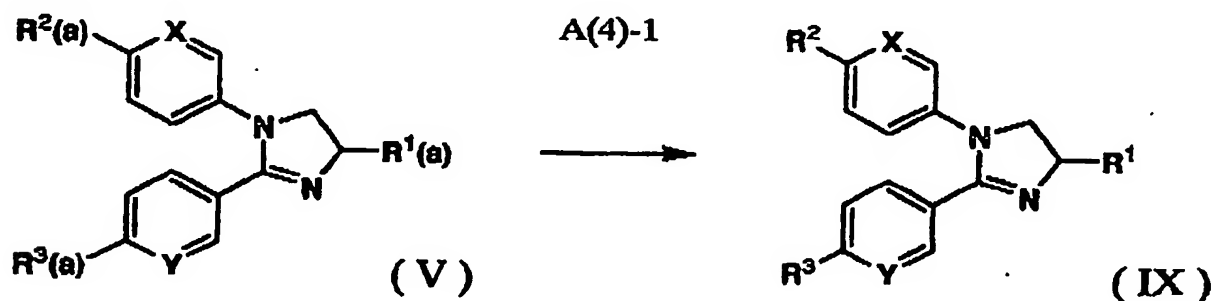
Process A(3)



In the above formulae, R represents H, (lower)alkyl or aryl[(lower)alkyl] group, which is not specified. "Tf" represents trifluoromethanesulfonyl as protective group.

- 5 4,5-Dihydroimidazole compound (V) can be transformed into compound (IX) by the above mentioned functional group transformation.

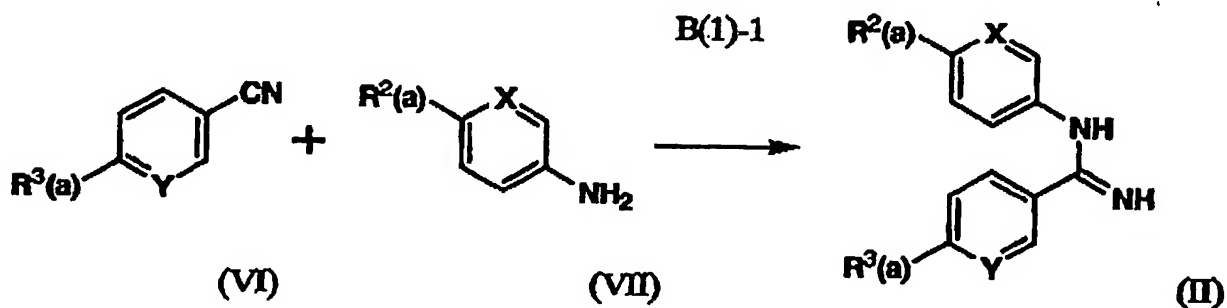
Process A(4)



- 10 Compound (IX) or pharmaceutically acceptable salts thereof also has an inhibiting activity against COX. So compound (IX) or salt thereof is also useful as medicament.

- 15 Compound (II) can be synthesized from compound (VI) and (VII) by following process other than purchase.

Process B(1)



- 20 In the above formulae, R²(a), R³(a), X and Y represent the same meanings as defined above.

Process B(1) is the process for preparing the compound (II), which is the starting material of Process A(1) and A(2).

Compound (VI) and (VII) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds, because the compounds as starting compound for synthesis of compound (II) have comparatively simple structure.

5 In this process, first, the solution of compound (VII) is added strong base.

The strong base employable in this process is not particularly limited and may include alkali metal hydrides such as lithium hydride, sodium hydride; alkali metal alkoxides such as lithium methoxide, sodium methoxide, sodium ethoxide, potassium t-butoxide; or the like.

10 The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane; amides such as N,N-dimethylformamide, dimethylacetamide, 15 hexamethylphosphoric triamide; sulfoxides such as dimethylsulfoxide; or the like.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from -10°C to room temperature, preferably room temperature.

20 The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 5min to 1hr, preferably from 10min to 40min.

Preferably, this process is carried out under inert gas such as nitrogen gas.

25 In this process, then the reaction mixture is added compound (VII).

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from -10°C to room temperature, preferably room temperature.

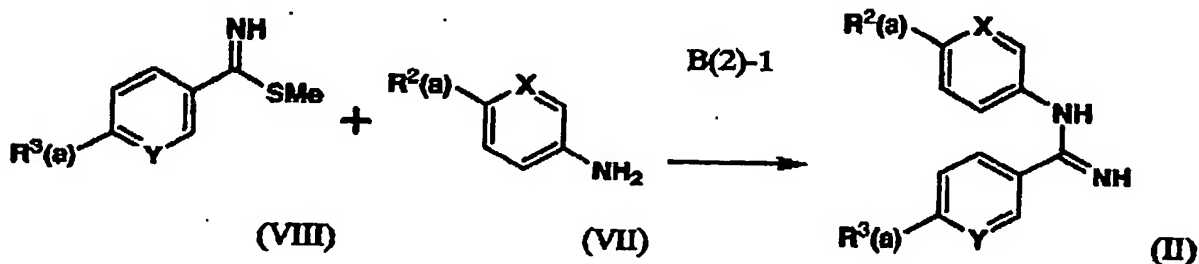
30 The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1hr to 24hrs, preferably from 2hrs to overnight.

After the reaction, the reaction mixture is poured into ice water

to decompose the excess strong base. Then, the desired compound may be collected by filtration as precipitate. Where necessary, it may be washed by solvent such as diisopropyl ether. Further, the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc, however, it may be used in the next step without further purification.

Compound (II) can be also synthesized from compound (VII) and (VIII) by following process other than purchase.

Process B(2)



In the above formulae, R²(a), R³(a), X and Y represent the same meanings as defined above.

Process B(2) is the another process for preparing the compound (II), in the case that R²(a) is the group such as [(lower)alkoxy]carbonyl or the like, which tends to be nucleophilically attacked more easily than cyano group.

In this process, compound (VII) and (VIII) are condensated in the acidic condition.

Compound (VII) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds.

Compound (VIII) may be synthesized by conventional method, that is, first the nitrile compound is led to thioamide compound by thioacetamide, and then methylated.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as alcohols such as methanol, ethanol, 2-propanol; ethers such

as diisopropyl ether, tetrahydrofuran, dioxane; and mixed solvent of these; or the like.

5 The acid for making acidic condition in this process is not particularly limited so long as it is used in a usual reaction as an acid catalyst and may include inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, or the like.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50°C to 150°C, preferably reflux condition.

10 The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 30min to 5hrs, preferably from 2hrs to 4hrs.

15 After the reaction, the reaction mixture is poured into basic water and extracted with organic solvent insoluble with water such as ethyl acetate. The organic layer is dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo. Where necessary, it may be washed by solvent such as diisopropyl ether. Further, the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc. however, it may be used in the
20 next step without further purification.

25 Above processes (Process A and B), all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method.

30 For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant,

suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

5

And on the commercial package comprising the pharmaceutical composition mentioned above and a written matter, which states above mentioned effects, is also useful.

10 While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general,
15 amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

The patents, patent applications and publications cited herein are incorporated by reference.

20

THE BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

25 Example 1-1

N^1 -(4-Bromophenyl)-4-methoxybenzamidine

Under Nitrogen gas, to a solution of 4-bromoaniline (3.88g, 22.5mmol) in dimethylsulfoxide (30ml) was added NaH (568mg, 23.7mmol) at room temperature. After the mixture was stirred for 30min,
30 4-methoxybenzonitrile (3.0g, 22.5mmol) was added.

The reaction mixture was stirred overnight then poured into 300ml

of ice-water. The precipitate was collected by filtration and washed with isopropyl ether to give 5.53g of desired compound as a white solid (80.4%).

5 IR (KBr, cm^{-1}) : 3473, 3357, 2958, 1612, 1249, 1174, 1103, 1074, 1030, 837.

NMR ($\text{DMSO}-d_6$, δ) : 3.80(3H, s), 6.32(2H, brs), 6.78(2H, d, $J=9\text{Hz}$), 6.96(2H, d, $J=9\text{Hz}$), 7.42(1H, d, $J=8\text{Hz}$), 7.92(2H, d, $J=8\text{Hz}$).

MS : 305 ($\text{M}+\text{H}$)⁺ (^{79}Br), 307 ($\text{M}+\text{H}$)⁺ (^{81}Br).

10

Example 1-2

1-(4-Bromophenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

15 To a mixture of N^1 -(4-Bromophenyl)-4-methoxybenzamidinium obtained by Example 1-1 (2.0g, 6.55mmol) and sodium bicarbonate (826mg, 9.83mmol) in 2-propanol (20ml) was added 3-bromo-1,1,1-trifluoro-2-propanone (2.0g, 10.5mmol). The reaction mixture was heated at 80°C for 2hrs.

The reaction mixture was cooled to room temperature and filtered.
20 The organic layer was evaporated in vacuo. The residue in acetic acid (20ml) was heated at 110°C for 2.5hrs.

The reaction mixture was poured into ice-water (100ml) and neutralized with sodium hydroxide aq. and extracted with ethyl acetate (50ml). The organic layer was washed with brine, dried by magnesium sulfate and evaporated in vacuo. The residue was purified by silica
25 gel column chromatography (20g) eluting with n-hexane/ethyl acetate (10/1) and washed with diisopropyl ether to give 660mg of desired compound (25.4%).

30 MP : 140-141°C.

IR (KBr, cm^{-1}) : 3140, 2970, 1487, 1294, 1252, 1149, 1122, 1026, 833.

NMR ($\text{DMSO}-d_6$, δ) : 3.75(3H, s), 6.92(2H, d, $J=9\text{Hz}$), 7.27(2H, d, $J=9\text{Hz}$).

7.36(2H, d, J=9Hz), 7.71(2H, d, J=2Hz), 8.18(1H, s).

MS : 397 (M+H)⁺ (⁷⁹Br), 399 (M+H)⁺ (⁸¹Br).

Example 2-1

5 4-Methoxy-N¹-(2-Methoxy-5-pyridinyl)benzamidine

Reaction was carried out in a manner similar to Example 1-1 using 4-methoxybenzonitrile and 5-amino-2-methoxypyridine to give 4.57g of desired compound (78.8%).

10

IR (KBr, cm⁻¹) : 3452, 3334, 3205, 2946, 1606, 1483, 1273, 1246, 1176, 1028, 841.

15

NMR (DMSO-d₆, δ) : 3.80(3H, s), 3.82(3H, s), 6.36(2H, brs), 6.76(1H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.20(1H, dd, J=9Hz and 3Hz), 7.67(1H, d, J=3Hz), 7.94(2H, d, J=9Hz).

MS : 258 (M+H)⁺.

Example 2-2

20

2-(4-Methoxyphenyl)-1-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H-imidazole hydrochloride

Reaction was carried out in a manner similar to Example 1-2 using 4-methoxy-N¹-(2-Methoxy-5-pyridinyl)benzamidine obtained by Example 2-1 to give 2-(4-methoxyphenyl)-1-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H-imidazole.

25

And then the product obtained was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give 399mg of desired compound as a white amorphous solid (14.7%).

30

NMR (DMSO-d₆, δ) : 3.75(3H, s), 3.89(3H, s), 6.80-7.05(3H, m), 7.31(2H, d, J=9Hz), 7.43(1H, d, J=9Hz), 7.74(1H, dd, J=9Hz and 2Hz), 8.17(1H, s), 8.27(1H, s).

MS : 350 (M+H)⁺ (free).

Example 3-1

N¹-(4-Methoxyphenyl)-2-methoxy-5-amidinopyridine

5

Under Nitrogen gas, to a solution of p-anisidine (2.75g, 22.4mmol) in tetrahydrofuran (15ml) was added dropwise 1.0M sodium bis(trimethylsilyl)amide in tetrahydrofuran (23.5ml, 23.5mmol) at room temperature. After the mixture was stirred for 20min,
10 6-methoxynicotinonitrile (3.0g, 22.4mmol) was added.

The reaction mixture was stirred for 4hrs, then poured into 300ml of ice-water. The precipitate was collected by filtration, washed with diisopropyl ether to give 3.36g of desired compound (58.4%) (mixture).

This material was used without further purification.

15

NMR (DMSO-d₆, δ) : 3.73(3H, s), 3.90(3H, s), 6.27(2H, brs), 6.70-7.00(5H, m), 8.24(1H, dd, J=9Hz and 2Hz), 8.72(1H, d, J=2 Hz).

MS : 258 (M+H)⁺.

20

Example 3-2

1-(4-Methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H-imidazole

25

Reaction was carried out in a manner similar to Example 1-2 using N¹-4-methoxy-2-methoxy-5-amidinopyridine obtained by Example 3-1 to give 526.6mg of desired compound as a colorless crystal (21.5%).

MP : 90-92°C.

IR (KBr, cm⁻¹) : 3141, 3107, 1604, 1518, 1294, 1248, 1159, 1118, 835.

30

NMR (DMSO-d₆, δ) : 3.81(3H, s), 3.83(3H, s), 6.81(1H, d, J=9Hz), 7.05(2H, d, J=9Hz), 7.38(2H, d, J=9Hz), 7.65(1H, dd, J=9Hz and 2Hz), 8.08(1H, d, J=2Hz), 8.17(1H, s).

MS : 350 (M+H)⁺.

Example 4-1

4-Cyano-4,5-dihydro-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-
1H-imidazole

To a suspension of N¹-4-Methoxy-2-methoxy-5- amidinopyridine obtained by Example 3-1 in tetrahydrofuran (20ml) were added 2-chloroacrylonitrile and diisopropylethylamine successively. The reaction mixture was heated at 70°C. After 5hrs, an additional 1.07ml of 2-chloroacrylonitrile was added and refluxed overnight.

The reaction mixture was cooled to room temperature, filtered and the solvent was removed in vacuo. The crude mixture was purified by silica gel column chromatography (24g) eluting with ethyl acetate to give 460mg of desired compound (54.9%).

This material was used in Example 4-2 without further purification.

Example 4-2

4-Cyano-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

A suspension of the residue obtained by Example 4-1 and manganese(IV) oxide (MnO₂) (1.3g, 10eq) in toluene (10ml) was heated at 85°C for 5.5hrs. To the reaction mixture was added manganese(IV) oxide (0.65g, 5eq) and heated at 110°C for 3hrs.

After cooling, the mixture was filtered through a Celite. The organic fraction was concentrated (396mg). The crude mixture was purified by silica gel column chromatography (12g) eluting with chloroform/methanol (50/1→15/1) and washed with diisopropyl ether to give 200.8mg of desired compound as a colorless solid (24.1%, through Example 4-1 and 4-2).

MP : 130-132°C.

IR (KBr, cm^{-1}) : 3132, 2949, 2233, 1604, 1516, 1466, 1292, 1254, 1024, 835.

NMR ($\text{DMSO}-d_6$, δ) : 3.81(3H, s), 3.84(3H, s), 6.81(1H, d, $J=9\text{Hz}$), 7.06(2H, d, $J=9\text{Hz}$), 7.37(2H, d, $J=9\text{Hz}$), 7.62(1H, dd, $J=9\text{Hz}$ and 2Hz), 8.10(1H, d, $J=2\text{Hz}$), 8.47(1H, s).

MS : 307 ($\text{M}+\text{H}$) $^+$.

Example 5-1

N^1 -(4-Benzyloxyphenyl)-2-methoxy-5-amidinopyridine

Reaction was carried out in a manner similar to Example 3-1 using 4-benzyloxyaniline hydrochloride to give 8.7g of desired compound (71.7%).

IR (KBr, cm^{-1}) : 3488, 3396, 3031, 2958, 1635, 1502, 1373, 1236, 1103, 1020, 840.

NMR ($\text{DMSO}-d_6$, δ) : 3.90(3H, s), 5.06(2H, s), 6.28(2H, brs), 6.70-7.05(5H, m), 7.25-7.60(5H, m), 8.24(1H, dd, $J=9\text{Hz}$ and 2Hz), 8.72(1H, d, $J=2\text{Hz}$).

MS : 334 ($\text{M}+\text{H}$) $^+$.

Example 5-2

1-(4-Benzyloxyphenyl)-2-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H-imidazole

Reaction was carried out in a manner similar to Example 1-2 using N^1 -(4-Benzyloxyphenyl)-2-methoxy-5-amidinopyridine obtained by Example 5-1 to give 2.27g of desired compound (44.5%).

IR (KBr, cm^{-1}) : 3064, 2950, 1290, 1244, 1157, 1122, 1022, 835.

NMR ($\text{DMSO}-d_6$, δ) : 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, $J=9\text{Hz}$), 7.05-7.58(9H, m), 7.65(1H, dd, $J=9\text{Hz}$ and 2Hz), 8.08(1H, d, $J=2\text{Hz}$), 8.17(1H, s).

MS : 426 (M+H)⁺.

Example 6

1-(4-Hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H
5 -imidazole

To a solution of

1-(4-benzyloxyphenyl)-2-(2-methoxy-5-pyridinyl)-
4-trifluoromethyl-1H-imidazole obtained by Example 5-2 (2.25g,
10 5.29mmol) in cyclohexene (22ml) and ethanol (45ml) was added 20%
palladium hydroxide on carbon (550mg). The resulting mixture was
stirred at reflux for 2hrs.

After cooling to room temperature, the mixture was filtered through
Celite and washed with ethanol. The filtrate was concentrated in vacuo,
15 and then the residue was washed with diisopropyl ether to give 1.31g
of desired compound as a white solid (73.9%).

MP : 198-200°C.

IR (KBr, cm⁻¹) : 3600-2600, 1469, 1292, 1247, 1159, 1126, 833.

20 NMR (CDCl₃, δ) : 3.91(3H, s), 6.67(1H, brs), 6.73(1H, d, J=9Hz), 6.87(2H,
d, J=9Hz), 7.11(2H, d, J=9Hz), 7.43(1H, s), 7.86(1H, dd, J=9Hz and 2Hz),
8.03(1H, d, J=2Hz).

MS : 336 (M+H)⁺.

25 Example 7

2-(2-Methoxy-5-pyridinyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-
4-trifluoromethyl-1H-imidazole

To the mixture of 1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-
30 4-trifluoromethyl-1H-imidazole obtained by Example 6 (600mg, 1.79mmol)
and triethylamine (190mg, 1.88mmol) in chloroform (12ml) was added
trifluoromethanesulfonic anhydride dropwise at an ice bath temperature

and stirred for 4.5hrs.

Sodiumhydrogencarbonate aq. (10ml) was added to quench the reaction. The reaction mixture was partitioned between chloroform and water. The organic layer was washed with water and then brine, dried by magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (10g) eluting with n-hexane/ethyl acetate (10/1) to give 593mg of desired compound (70.9%).

IR (KBr, cm^{-1}) : 3118, 3062, 1421, 1255, 1219, 1136, 891.

NMR (CDCl_3 , δ) : 3.92(3H, s), 6.71(1H, d, $J=9\text{Hz}$), 7.30-7.48(4H, m), 7.50(1H, s), 7.66(1H, dd, $J=9\text{Hz}$ and 2Hz), 8.08(1H, d, $J=2\text{Hz}$).

MS : 467 ($\text{M}+\text{H}$) $^+$.

Example 8

1-(4-Cyanophenyl)-2-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H-imidazole

To a solution of 2-(2-methoxy-5-pyridinyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-4-trifluoromethyl-1H-imidazole obtained by Example 7 (150mg, 0.321mmol) in N,N-dimethylformamide (7.5ml) were added zinc cyanide ($\text{Zn}(\text{CN})_2$) (38mg, 0.321mmol) and tetrakis(triphenylphosphine)palladium ($\text{Pd}(\text{PPh}_3)_4$) (185mg, 0.16mmol) at ambient temperature under nitrogen gas. The mixture was stirred at 85°C for 2days.

The mixture was cooled to room temperature and partitioned between ethyl acetate (50ml) and water (50ml). The organic layer was washed with water and brine, then dried by magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (20g) eluting with toluene/ethyl acetate (10:1) and washed with diisopropyl ether to give 57.2mg of desired compound as a white solid (51.8%).

MP : 155-158°C.

IR (KBr, cm^{-1}) : 3120, 2250, 1606, 1250, 1122, 822.

NMR ($\text{DMSO}-d_6$, δ) : 3.85(3H, s), 6.82(1H, d, $J=9\text{Hz}$), 7.61(1H, dd, $J=9\text{Hz}$ and 2Hz), 7.65(2H, d, $J=9\text{Hz}$), 8.03(2H, d, $J=9\text{Hz}$), 8.12(1H, d, $J=2\text{Hz}$), 8.36(1H, s).

MS : 345 ($\text{M}+\text{H}$)⁺.

Example 9

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of N^1 -(4-methoxyphenyl)-4-methoxybenzamidinium (0.65 g), ethyl bromopyruvate (0.64 ml) and sodium hydrogencarbonate (0.85 g) in ethanol (7 ml) was stirred at reflux condition for overnight.

After cooling to room temperature, the reaction mixture was filtrated and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (5/1→2/1) to give 244mg of desired compound as an oil (27.3%).

IR (Neat, cm^{-1}) : 3437, 3392, 3367, 3217, 3140, 3072, 2966, 2843, 1803, 1699, 1651, 1614.

NMR ($\text{DMSO}-d_6$, δ) : 1.29(3H, t, $J=7.1\text{Hz}$), 3.74(3H, s), 3.80(3H, s), 4.27(2H, q, $J=7.1\text{Hz}$), 6.88(2H, dd, $J=6.8\text{Hz}$ and 2.1Hz), 7.02(2H, dd, $J=6.7\text{Hz}$ and 2.1Hz), 7.26 (2H, dd, $J=5.0\text{Hz}$ and 2.1Hz), 7.28 (2H, dd, $J=6.7\text{Hz}$ and 2.1Hz), 8.02 (1H, s).

MS : 353 ($\text{M}+\text{H}$)⁺.

Example 10

4-Carbamoyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of 4-ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 9 (244mg) and sodium methoxide (112mg) in formamide (2ml) was stirred at 100°C for 2hrs.

After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1→0/1) to give 73mg of desired compound (32.6%).

MP : 167-169°C.

IR (KBr, cm^{-1}): 3427, 3342, 3276, 3155, 2964, 2841, 1672, 1610.

NMR (DMSO- d_6 , δ) : 3.74(3H, s), 3.80(3H, s), 6.87-6.89(2H, m), 7.00-7.03(2H, m), 7.20(1H, s), 7.26-7.29(4H, m), 7.43(1H, s), 7.77(1H, s).

MS : 324 (M+H)⁺.

Example 11

4-Cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

A mixture of 4-carbamoyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 10 (73mg) and phosphorus oxychloride (63 μ l) in N,N-dimethylformamide (1ml) was stirred at room temperature for 1hr.

The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (2/1).

After correcting the fraction, the solvent was removed by evaporation and the residue was dissolved in ethyl acetate (1ml). 4N Hydrochloride/ethyl acetate (56ml) was added to the above solution. Resulting precipitates were corrected by filtration and washed with

isopropyl ether to give 38mg of desired compound (49.2%).

MP : 142-143°C.

IR (KBr, cm^{-1}): 3425, 3407, 3132, 3076, 3043, 3026, 2962, 2929, 2835,
2231, 1608.

NMR ($\text{DMSO}-d_6$, δ) : 3.74(3H, s), 3.80(3H, s), 6.55(1H, s), 6.88-6.91(2H, m), 7.03-7.05(2H, m), 7.25-7.32(4H, m), 8.39(1H, s).

MS : 306 (free) ($\text{M}+\text{H}$)⁺.

Example 12-1

4-Cyano-4,5-dihydro-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of N¹-(4-methoxyphenyl)-4-methoxybenzamidine (5g),
2-chlorocyclohexene (2.01ml) and N,N-diisopropylethylamine (4.38 ml) in tetrahydrofuran (100ml) was stirred at reflux condition for 6hrs. Additional 2-chlorocyclohexene (2.01ml) was added, the mixture was refluxed for overnight.

After cooling to room temperature, the reaction mixture was
evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 3.28 g of desired compound as an oil (63.7%).

IR (Neat, cm^{-1}) : 3283, 3217, 3114, 3055, 3003, 2958, 2839, 2243, 2048,
1896, 1732, 1606.

NMR ($\text{DMSO}-d_6$, δ) : 3.70(3H, s), 3.74(3H, s), 4.11-4.19(2H, m), 5.20(1H, dd, J=10.5Hz and 8.2Hz), 6.81-6.97(6H, m), 7.32-7.37(2H, m).

MS : 308 ($\text{M}+\text{H}$)⁺.

Example 12-2

4-Cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A suspension of 4-cyano-4,5-dihydro-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 12-1 (2.7g) and manganese(IV) oxide (MnO_2) (3.82 g) in N,N-dimethylformamide (30ml) was stirred at 100°C for 4hrs.

5 After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. To the solution of the residue in N,N-dimethylformamide (30ml), phosphorus oxychloride (2.46ml) was added under stirring at 0°C.

10 After stirring at room temperature for 1hr, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo to give 2.11g of desired compound (78.7%).

15 MP : 132-134°C.

NMR ($\text{DMSO}-d_6$, δ) : 3.74(3H, s), 3.80(3H, s), 6.87-6.93(2H, m), 7.02-7.08(2H, m), 7.23-7.34(4H, m), 8.39(1H, s).

MS : 306 ($\text{M}+\text{H}$)⁺.

20 Example 13

4-Cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

25 4N Hydrochloride/ethyl acetate (254 μl) was added to a solution of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 12-2 (300mg) in ethyl acetate (1ml). Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 300mg of desired compound (86.4%).

30 MP : 142-143°C.

IR (KBr , cm^{-1}) : 3425, 3407, 3132, 3076, 3043, 3026, 2962, 2929, 2835, 2231, 1608.

NMR (DMSO- d_6 , δ) : 3.74(3H, s), 3.80(3H, s), 6.55(1H, s), 6.88-6.91(2H, m), 7.03-7.05(2H, m), 7.25-7.32(4H, m), 8.39(1H, s).
MS : 306 (free) (M+H)⁺.

5 **Example 14**

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

10 A mixture of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (315mg) and 4N hydrochloride/ethanol (6.2ml) was stirred at reflux condition for 1hr.

15 After cooling to room temperature, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.26g of desired compound (71.5%).

MP : 142-143°C.

20 IR (Neat, cm^{-1}) : 3437, 3392, 3367, 3217, 3140, 3072, 2966, 2843, 1803, 1699, 1651, 1614.

NMR (DMSO- d_6 , δ) : 1.29(3H, t, J=7.1Hz), 3.74(3H, s), 3.80(3H, s), 4.27(2H, q, J=7.1Hz), 6.88(2H, dd, J=6.8Hz and 2.1Hz), 7.02(2H, dd, J=6.7Hz and 2.1Hz), 7.26(2H, dd, J=5.0Hz and 2.1Hz), 7.28(2H, dd, J=6.7Hz and 2.1Hz), 8.02(1H, s).

25 MS : 353 (M+H)⁺.

Example 15

4-Hydroxymethyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

30

1N Diisopropylaluminiumhydride in toluene (3.76ml) was added dropwise to a solution of 4-ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-

methoxyphenyl)-1H-imidazole obtained by Example 14 (5ml) under stirring at -78°C, and stirred at -78°C for 2hrs.

The reaction mixture was quenched by sat. ammonium chloride aq., then 1N hydrochloric acid was added and extracted with water. The combined aqueous layer was neutralized with sat. sodium hydrogencarbonate aq., and extracted with ethyl acetate, dried over magnesium sulfate. After evaporation of the solution, the residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.14g of desired compound (30%).

IR (Neat, cm^{-1}) : 3369, 3307, 3224, 3076, 3006, 2939, 2837, 1676, 1608.
NMR (DMSO- d_6 , δ) : 3.73(3H, s), 3.79(3H, s), 4.42(2H, d, $J=5.6\text{Hz}$), 4.96(1H, t, $J=5.6\text{Hz}$), 6.85(2H, d, $J=8.8\text{Hz}$), 7.00(2H, d, $J=8.9\text{Hz}$), 7.15-7.25(5H, m).
MS : 311 (M+H)⁺.

Example 16

4-Formyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole.

Dimethylsulfoxide (125 μ l) was added to a solution of oxalylchloride (118 μ l) in dichloromethane (2ml) under stirring at -78°C. After stirred at -78°C for 10min, a solution of 4-hydroxymethyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 15 (0.21g) in dichloromethane (2ml) was added and stirred at -78°C for 1hr.

Triethylamine (0.66ml) was added to the reaction mixture, and stirred at 0°C for 20min.

The mixture was quenched by sat. ammonium chloride aq., and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo to give 120mg of desired compound as an oil (57.5%).

IR (Neat, cm^{-1}) : 3126, 3057, 3005, 2960, 2837, 2760, 2551, 2048, 1685, 1610.

NMR (CDCl₃, δ) : 3.83(3H, s), 3.86(3H, s), 6.81(2H, dd, J=6.9Hz and 2.0Hz), 6.94(2H, dd, J=6.8Hz and 2.1Hz), 7.16(2H, dd, J=6.7Hz and 2.2Hz), 7.36(2H, dd, J=6.7Hz and 2.1Hz), 7.16(1H, s), 9.98(1H, s).

MS : 309 (M+H)⁺.

5

Example 17

4-Difluoromethyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

10 Diethylaminosulfur trifluoride (154 μ l) was added to a solution of 4-formyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 16 (120mg) in dichloromethane (2ml) under stirring at 0°C.

15 After stirring at room temperature for overnight, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1). After correcting the fraction, the solvent was removed by evaporation and
20 the residue was dissolved in ethyl acetate (1ml). 4N hydrochloride/ethyl acetate (97 μ l) was added. Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 24mg of desired compound (16.8%).

25 MP : 150-153°C.

IR (KBr, cm⁻¹) : 3454, 3433, 3265, 3101, 3060, 2958, 2837, 2735, 2659, 2563, 1606.

NMR (DMSO-d₆, δ) : 3.76(3H, s), 3.80(3H, s), 6.84(1H, t, J=56.2Hz), 6.91-6.97(2H, s), 7.02-7.08(2H, m), 7.28-7.38(4H, m), 7.93 (1H, t, J=2.2Hz).

30

MS : 331 (free) (M+H)⁺.

Example 18

4-Carboxy-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (1.5g) in 50% sulfuric acid (16ml) was stirred at reflux condition for 1hr.

After cooling to room temperature, the reaction mixture was poured into 6% sodium hydroxide aq. (100ml), and washed with ethyl acetate. The aqueous layer was acidified by conc. hydrochloric acid and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were corrected by filtration and washed with isopropyl ether to give 1.18g of desired compound (74.1%).

MP : 102-105°C.

IR (KBr, cm^{-1}) : 3427, 3269, 3174, 3141, 3086, 3005, 2965, 2910, 2839, 1678, 1610.

NMR (DMSO- d_6 , δ) : 3.76(3H, s), 3.813(3H, s), 6.89(2H, dt, $J=7.0\text{Hz}$ and 2.0Hz), 7.03(2H, dt, $J=7.2\text{Hz}$ and 2.0Hz), 7.26-7.32(4H, m), 7.97(1H, s).

MS : 325 ($M+H$) $^+$.

Example 19

4-Ethylmethycarbamoyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of 4-carboxy-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 18 (170mg), N-ethylmethylaniline (45 μl), 1-hydroxybenzotriazole (71mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100mg) in N,N-dimethylformamide (5ml) was stirred at room temperature for overnight.

The reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The

residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1). The resulting precipitates were corrected by filtration and washed with isopropyl ether to give 72mg of desired compound (37.6%).

5

MP : 138-139 °C.

IR (KBr, cm^{-1}) : 3124, 3068, 3006, 2966, 2929, 2841, 1603.

NMR (DMSO- d_6 , δ) : 1.05-1.29(3H, m), 2.91-3.03(2H, m), 3.33-3.56(2H, m), 3.74(3H, s), 3.80(3H, s), 3.91-4.06(1H, m), 6.88(2H, dt, $J=8.8\text{Hz}$ and 1.8Hz), 7.02(2H, dt, $J=8.8\text{Hz}$ and 2.0Hz), 7.23-7.30(4H, m), 7.72(1H, s).

10

MS : 366 (M+H) $^+$.

Example 20

15 4-Cyclopropyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

A mixture of N^1 -(4-methoxyphenyl)-4-methoxybenzamidinium (1g), 2-bromo-1-cyclopropylethanone (1.27g) and sodium hydrogencarbonate (656mg) in 2-propanol (10ml) was stirred at reflux condition for overnight.

20

After cooling to room temperature, the reaction mixture was filtered off and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was dissolved in acetic acid (10ml), and refluxed for 1hr.

25

After cooling to room temperature, the mixture was poured into saturated sodium hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (3/1). After correcting the fraction, the solvent was removed by evaporation and the residue was dissolved in ethyl acetate (5ml).

30

4N hydrochloride/ethyl acetate (175 μ l) was added. Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 200mg of desired compound (14.4%).

5 MP : 180-181°C.

IR (KBr, cm⁻¹) : 3273, 3051, 2966, 2935, 2906, 2835, 2740, 2640, 2592, 1610.

NMR (DMSO-d₆, δ) : 0.88-0.96(2H, m), 1.00-1.07(2H, m), 2.02-2.11(2H, m), 3.79(3H, s), 3.80(3H, s), 7.00-7.11(4H, m), 7.35-7.41(4H, m),
10 7.67(1H, s).

MS : 321 (free) (M+H)⁺.

Example 21

15 1-(4-Methoxyphenyl)-2-(4-methoxyphenyl)-4-methyl-1H-imidazole
hydrochloride

85mg of desired compound was obtained from N¹-(4-methoxyphenyl)-4-methoxybenzamidinium (200mg) and 1-bromoacetone (204 μ l) in the similar manner to that of Example 20.

20 MP : 203-205°C.

IR (KBr, cm⁻¹) : 3400, 3114, 3055, 2966, 2929, 2833, 2804, 2711, 2650, 2578, 2426, 1612.

NMR (DMSO-d₆, δ) : 2.39(3H, s), 3.79(3H, s), 3.81(3H, s), 7.02-7.12(4H, m), 7.36-7.66(4H, m), 7.66(1H, s), 14.6-15.5(1H, br).
25

MS : 295 (free) (M+H)⁺.

Example 22-1

30 N¹-(4-Ethoxycarbonylphenyl)-4-methoxybenzamidinium

A mixture of methyl 4-methoxybenzenecarbimidothioate hydroiodide (3.9g), ethyl 4-aminobenzoate (2.08g) and acetic acid (2ml) in

2-propanol (40ml) was stirred at reflux condition for 2hrs.

After cooling to room temperature, the reaction mixture was poured into saturated sodium hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo.

5 Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 2.35g of desired compound (62.4%).

MP : 128-132°C.

IR (KBr, cm^{-1}) : 3456, 3305, 3251, 3178, 2976, 2933, 2850, 1711, 1626.

10 NMR (DMSO- d_6 , δ) : 1.31(3H, t, $J=7.1\text{Hz}$), 3.81(3H, s), 4.28(2H, q, $J=7.1\text{Hz}$), 6.46(2H, s), 6.90-7.01(4H, m), 7.86-7.91(4H, m).

MS : 299 (M+H) $^+$.

Example 22-2

15 1-(4-Ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

A mixture of N¹-(4-Ethoxycarbonylphenyl)-4-methoxybenzamidinium obtained by Example 22-1 (0.5g), 3-bromo-1,1,1-trifluoro-2-propanone (0.35ml) and sodium hydrogencarbonate (563mg) in 2-propanol (5ml) was
20 stirred at reflux condition for 4hrs.

After cooling to room temperature, the reaction mixture was filtered off and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and
25 evaporated in vacuo. The residue was dissolved in acetic acid (10ml), and refluxed for 1hr.

After cooling to room temperature, the mixture was poured into saturated sodium hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was
30 purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (3/1) to give 0.53g of desired compound as an oil (81%).

IR (Neat, cm^{-1}) : 3745, 3610, 3435, 3396, 3365, 3298, 3280, 3236, 3130, 2962, 2927, 2856, 1693, 1649.

NMR ($\text{DMSO}-d_6$, δ) : 1.33(3H, t, $J=7.1\text{Hz}$), 3.75(3H, s), 4.34(2H, q, $J=7.1\text{Hz}$), 6.91(2H, dd, $J=6.9\text{Hz}$ and 1.9Hz), 7.26(2H, dd, $J=6.8\text{Hz}$ and 2.0Hz), 7.53
5 (2H, dd, $J=6.8\text{Hz}$ and 1.7Hz), 8.04 (2H, dd, $J=6.7\text{Hz}$ and 1.8Hz), 8.25 (1H, d, $J=1.2\text{Hz}$).

MS : 391 ($\text{M}+\text{H}$) $^+$.

Example 23

10 1-(4-Carbamoylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

255mg of desired compound was obtained from
1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1
15 H-imidazole obtained by Example 22-2 (710mg) in the similar manner to that of Example 10.

IR (KBr, cm^{-1}) : 3410, 3303, 3190, 3122, 2960, 2841, 1655, 1614.

NMR ($\text{DMSO}-d_6$, δ) : 3.77(3H, s), 6.90(2H, dt, $J=8.8\text{Hz}$ and 2.0Hz), 7.26(2H, dt, $J=8.8\text{Hz}$ and 2.1Hz), 7.46(2H, d, $J=8.5\text{Hz}$), 7.52(1H, s), 7.96(2H, d, $J=8.5\text{Hz}$), 8.10(1H, s), 8.21(1H, d, $J=1.2\text{Hz}$).
20

MS : 362 ($\text{M}+\text{H}$) $^+$.

Example 24

25 1-(4-Cyanophenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

A mixture of 1-(4-carbamoylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole obtained by Example 23 (200mg) and
30 phosphorus oxychloride (0.16ml) in N,N-dimethylformamide (2ml) was stirred at room temperature for 1hr.

The reaction mixture was poured into saturated sodium

hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 171mg of desired compound (90%).

5

MP : 146-148°C.

IR (KBr, cm^{-1}) : 3415, 3163, 3118, 3064, 3012, 2968, 2906, 2839, 2229, 1608.

10 NMR (DMSO- d_6 , δ) : 3.76(3H, s), 6.92(2H, dt, J=8.9Hz and 1.9Hz), 7.25(2H, dt, J=8.7Hz and 2.0Hz), 7.60(2H, dt, J=8.5Hz and 1.8Hz), 8.00(2H, dt, J=8.6Hz and 1.7Hz), 8.27(1H, d, J=1.1Hz).

MS : 344 (M+H)⁺.

Example 25-1

15 4-Cyano-4,5-dihydro-1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-1H-imidazole

265mg of desired compound was obtained from N¹-(4-ethoxycarbonylphenyl)-4-methoxybenzamidinium (500 mg) in the similar manner to that of Example 12-1.

20

IR (Neat, cm^{-1}) : 3417, 3253, 3217, 3068, 2974, 2902, 2841, 1711, 1603.

NMR (DMSO- d_6 , δ) : 1.28(3H, t, J=7.1Hz), 3.78(3H, s), 4.26(2H, q, J=7.1Hz), 4.31-4.46(2H, m), 5.27(1H, t, J=9.9Hz), 6.88-6.97(4H, m), 7.37(2H, dt,

25 J=8.8Hz and 1.9Hz), 7.79 (2H, dt, J=8.7Hz and 1.9Hz).

MS : 350 (M+H)⁺.

Example 25-2

4-Cyano-1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-1H-imidazole

30 e

A suspension of 4-cyano-4,5-dihydro-1-(4-ethoxycarbonylphenyl)-

2-(4-methoxyphenyl)-1H-imidazole obtained by Example 25-1 (0.26g) and manganese(IV) oxide (MnO_2) (259 mg) in ethyl acetate (5 ml) was stirred at reflux condition for overnight.

5 After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (5/1) to give 117mg of desired compound (45.3%).

10 MP : 139-140°C.

IR (KBr, cm^{-1}) : 3425, 3143, 3060, 2979, 2947, 2902, 2839, 2235, 1718, 1606.

NMR ($\text{DMSO}-d_6$, δ) : 1.33(3H, t, $J=7.1\text{Hz}$), 3.75(3H, s), 4.34(2H, q, $J=7.1\text{Hz}$), 6.90(2H, dt, $J=8.8\text{Hz}$ and 1.9Hz), 7.25(2H, dt, $J=8.8\text{Hz}$ and 1.9Hz), 7.52(2H, dt, $J=8.5\text{Hz}$ and 1.7Hz), 8.05(2H, dt, $J=8.5\text{Hz}$ and 1.7Hz), 8.55(1H, s).

15 MS : 348 ($\text{M}+\text{H}$) $^+$.

Example 26

1-(4-Carbamoylphenyl)-4-cyano-2-(4-methoxyphenyl)-1H-imidazole

20

49mg of desired compound was obtained from 4-cyano-1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 25-2 (100mg) in the similar manner to that of Example 10 (53.5%).

25 MP : 228-290 °C.

IR (KBr, cm^{-1}) : 3456, 3396, 3354, 3292, 3172, 3113, 3051, 2970, 2837, 2227, 1682, 1612.

NMR ($\text{DMSO}-d_6$, δ) : 3.75(3H, s), 6.91(2H, d, $J=8.8\text{Hz}$), 7.26(2H, d, $J=8.8\text{Hz}$), 7.46(2H, d, $J=8.5\text{Hz}$), 7.54(1H, s), 7.97(2H, d, $J=8.5\text{Hz}$), 8.11(1H, s), 8.52(1H, s).

30

MS : 319 ($\text{M}+\text{H}$) $^+$.

Example 27

4-Cyano-1-(4-cyanophenyl)-2-(4-methoxyphenyl)-1H-imidazole

24mg of desired compound was obtained from 1-(4-carbamoylphenyl)-
4-Cyano-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 26
(40mg) in the similar manner to that of Example 24 (63.6%).

MP : 185-186 °C

IR (KBr, cm^{-1}) : 3419, 3219, 3132, 3091, 3057, 3012, 2968, 2935, 2837,
2229, 1608.

NMR (DMSO- d_6 , δ) : 3.76(3H, s), 6.92(2H, d, J=8.8Hz), 7.25(2H, d, J=8.7Hz),
7.59(2H, d, J=8.5Hz), 8.02(2H, d, J=8.5Hz), 8.56(1H, s).

MS : 301 (M+H)⁺.

Example 28

4-Acetyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

3N solution of methylmagnesium bromide in diethyl ether (1.17ml)
was added to a solution of 4-cyano-1-(4-methoxyphenyl)-2-(4-
methoxyphenyl)-1H-imidazole (357mg) in tetrahydrofuran (5ml).

After stirring at room temperature for 2hrs, the reaction mixture
was poured into hydrochloric acid and extracted with ethyl acetate,
washed with water, dried over magnesium sulfate and evaporated in vacuo.
The residue was purified by silica gel column chromatography eluting
with n-hexane/ethyl acetate (5/1) to give 258mg of desired compound
(68.5%).

MP : 116-117°C

IR (KBr, cm^{-1}) : 3431, 3118, 3066, 3008, 2964, 2929, 2837, 1668, 1610.

NMR (DMSO- d_6 , δ) : 2.48(3H, s), 3.74(3H, s), 3.80(3H, s), 6.89(2H,
d, J=8.6Hz), 7.03(2H, d, J=8.8Hz), 7.26-7.31(4H, m), 8.12(1H, s).

MS : 323 (M+H)⁺.

Example 29-1

4-Ethoxycarbonyl-4,5-dihydro-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

5

A mixture of N¹-(4-benzyloxyphenyl)-4-methoxybenzamidine (1.25g), ethyl 2-chloroacrylate (0.76g) and N,N-diisopropylethylamine (0.98ml) in tetrahydrofuran (12ml) was stirred at reflux condition for 2hrs.

10 After cooling to room temperature, the reaction mixture was filtered off and the filtrate was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo.

This material was used in the next step without further purification.

Example 29-2

15 4-Ethoxycarbonyl-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

The residue of Example 29-1 was dissolved in N,N-dimethylformamide (10ml), and manganese(IV) oxide (1.63g) was added to the solution.

20 After stirring at 100°C for 4hrs, the reaction mixture was cooled to room temperature and poured into water and ethyl acetate. After filtration, the mixture was extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate
25 (1/1) to give 1.5g of desired compound as an oil (93.1%).

IR (Neat, cm⁻¹) : 3433, 3253, 3224, 3140, 3064, 2966, 2843, 1722, 1712, 1606.

30 NMR (DMSO-d₆, δ) : 1.29(3H, t, J=7.1Hz), 3.75(3H, s), 4.27(2H, d, J=7.1Hz), 5.15(2H, s), 6.88(2H, dt, J=8.9Hz and 1.9Hz), 7.10(2H, dt, J=8.9Hz and 1.9Hz), 7.24-7.49(9H, m), 8.04(1H, s).

MS : 429 (M+H)⁺.

Example 30

1-(4-Benzoyloxyphenyl)-4-formyl-2-(4-methoxyphenyl)-1H-imidazole

5 0.95N Diisopropylaluminiumhydride in toluene (6.49ml) was added dropwise to a solution of 4-ethoxycarbonyl-1-(4-benzoyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 29-2 (0.88g) in dichloromethane (5ml) under stirring at -78°C, and stirred at -78°C for 2hrs.

10 The reaction mixture was quenched by sat. ammonium chloride aq., then 1N hydrochloric acid was added and extracted with water. After sodium hydroxide aq. was added, extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo.

15 The residue was dissolved in N,N-dimethylformamide (10ml), and manganese(IV) oxide (1.79g) was added to the solution.

20 After stirring at 100°C for 1hr, the reaction mixture was cooled to room temperature and poured into water and ethyl acetate. After filtration, the mixture was extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.77g of desired compound as an oil (97.5%).

IR (Neat, cm^{-1}) : 3440, 3361, 3219, 3124, 3062, 2937, 2837, 2760, 1732, 1684, 1610.

25 NMR ($\text{DMSO}-d_6$, δ) : 3.75(3H, s), 5.16(2H, s), 6.89(2H, dt, $J=8.9\text{Hz}$ and 1.9Hz), 7.12(2H, dt, $J=8.9\text{Hz}$ and 2.1Hz), 7.27-7.49(9H, m), 8.28(1H, s), 9.82(1H, s).

MS : 385 ($\text{M}+\text{H}$)⁺.

30 Example 31

1-(4-Benzoyloxyphenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole

Diethylaminosulfur trifluoride (0.46 ml) was added to a solution of 1-(4-benzyloxyphenyl)-4-formyl-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 30 (0.45g) in dichloromethane (5ml) under stirring at 0°C.

After stirring at room temperature for overnight, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.38g of desired compound as an oil (79.9%).

IR (Neat, cm^{-1}) : 3433, 3155, 3113, 3066, 3041, 2964, 2841, 1732, 1610.

NMR (DMSO-d_6 , δ) : 3.74(3H, s), 5.15(2H, s), 6.87(2H, d, $J=8.9\text{Hz}$), 7.08(1H, t, $J=55.0\text{Hz}$), 7.10(2H, d, $J=8.9\text{Hz}$), 7.24-7.45(9H, m), 7.73(1H, t, $J=2.3\text{Hz}$).

MS : 407 ($\text{M}+\text{H}$)⁺.

Example 32

4-Difluoromethyl-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A suspension of 1-(4-benzyloxyphenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 31 (0.38g) and dry 20% palladium hydroxide on carbon ($\text{Pd}(\text{OH})_2/\text{C}$) (100mg) in ethanol (8ml) and cyclohexene (4ml) was stirred at reflux condition for 1hr and cooled to room temperature.

After filtration, the reaction mixture was evaporated in vacuo to give 0.3g of desired compound (ca.100%).

MP : 143-145°C

IR (KBr, cm^{-1}) : 3149, 3111, 3003, 2966, 2837, 2804, 2679, 2602, 1610.

NMR (DMSO- d_6 , δ) : 3.74(3H, s), 6.80-6.91(4H, m), 6.96(1H, t, $J=55.0\text{Hz}$), 7.14(2H, dt, $J=8.7\text{Hz}$ and 1.9Hz), 7.27(2H, dt, $J=8.9\text{Hz}$ and 1.9Hz), 7.68(1H, t, $J=2.2\text{Hz}$), 9.90(1H, s).

MS : 317 (M+H)⁺.

5

Example 33

4-Difluoromethyl-2-(4-methoxyphenyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole

10 Triethylamine (0.15ml) and trifluoromethanesulfonic anhydride (0.18ml) was added to a solution of 4-difluoromethyl-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 32 (300mg) in chloroform (5ml) under stirring at 0°C.

15 After stirring at 0°C for 4hrs, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.24g of desired compound as an oil (56.4%).

20

IR (Neat, cm^{-1}) : 3159, 3118, 3078, 3006, 2939, 2848, 1610.

NMR (DMSO- d_6 , δ) : 3.74(3H, s), 6.89(2H, dt, $J=8.9\text{Hz}$ and 1.9Hz), 7.01(1H, t, $J=54.8\text{Hz}$), 7.23(2H, dt, $J=8.9\text{Hz}$ and 2.0Hz), 7.54-7.69(4H, m), 7.92(1H, t, $J=2.3\text{Hz}$).

25 MS : 449 (M+H)⁺.

Example 34

1-(4-Cyanophenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole

30

A suspension of 4-difluoromethyl-2-(4-methoxyphenyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole obtained by Example

33 (0.2g) , zinc cyanide ($\text{Zn}(\text{CN})_2$) (55mg) and
tetrakis(triphenylphosphine)palladium ($\text{Pd}(\text{PPh}_3)_4$) (272mg) in
N,N-dimethylformamide (1ml) was stirred at 85°C for overnight under
nitrogen atmosphere then cooled to room temperature.

5 After filtration, the reaction mixture was poured into water and
extracted with ethyl acetate, dried over magnesium sulfate and
evaporated in vacuo. The residue was purified by silica gel column
chromatography eluting with n-hexane/ethyl acetate (1/1) to give 83mg
of desired compound (47.7%).

10 MP : $131-132^\circ\text{C}$.

IR (KBr, cm^{-1}) : 3222, 3157, 3114, 2966, 2839, 2231, 1610.

NMR ($\text{DMSO}-d_6$, δ) : 3.75(3H, s), 6.91(2H, dt, $J=8.9\text{Hz}$ and 1.9Hz), 7.02(1H,
t, $J=54.8\text{Hz}$), 7.24(2H, dt, $J=8.8\text{Hz}$ and 2.0Hz), 7.55 (2H; dt, $J=8.7\text{Hz}$
15 and 1.7Hz), 7.93(1H, t, $J=2.2\text{Hz}$), 7.95(2H, dt, $J=8.5\text{Hz}$ and 2.0Hz).

MS : 326 ($\text{M}+\text{H}$) $^+$.

Example 35-1

20 1-(4-Benzoyloxyphenyl)-4,5-dihydro-4-ethoxycarbonyl-2-(2-methoxy-5-
pyridinyl)-1H-imidazole

25 2.67g of desired compound was obtained from a mixture of
 N^1 -(4-benzoyloxyphenyl)-2-methoxy-5-amidinopyridine (2.57g) and ethyl
2-chloroacrylate (1.56g) in the similar manner to that of Example 12-1
(80.3%).

IR (Neat, cm^{-1}) : 3448, 3411, 3378, 3037, 2981, 2949, 2902, 1734, 1608.

NMR ($\text{DMSO}-d_6$, δ) : 1.24(3H, t, $J=7.1\text{Hz}$), 3.83(3H, s), 4.06(2H, d, $J=9.9\text{Hz}$),
4.17(2H, q, $J=7.1\text{Hz}$), 4.81(1H, t, $J=9.8\text{Hz}$), 5.04(2H, s), 6.77(1H, d,
30 $J=8.6\text{Hz}$), 6.93(4H, s), 7.29-7.44(5H, m), 7.68(1H, dd, $J=8.6\text{Hz}$ and 2.4Hz),
8.18(1H, d, $J=2.4\text{Hz}$).

MS : 432 ($\text{M}+\text{H}$) $^+$.

Example 35-2

1-(4-Benzoyloxyphenyl)-4-ethoxycarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

5

1.74g of desired compound was obtained from a suspension of 1-(4-benzoyloxyphenyl)-4,5-dihydro-4-ethoxycarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 35-1 (2.67g) in N,N-dimethylformamide (27ml) in the similar manner to that of Example 25-2 (65.5%).

10

MP : 109-110°C.

IR (KBr, cm^{-1}) : 3433, 3390, 3136, 3070, 2976, 2941, 2841, 1693, 1608.

NMR (DMSO- d_6 , δ) : 1.29(3H, t, J=7.1Hz), 3.84(3H, s), 4.28(2H, q, J=7.1Hz), 5.15(2H, s), 6.80(1H, d, J=8.6Hz), 7.12(2H, d, J=8.9Hz), 7.32-7.49(7H, m), 7.65(1H, dd, J=8.6Hz and 2.4Hz), 8.06(1H, d, J=2.4Hz), 8.12(1H, s).

15

MS : 430 (M+H)⁺.

20 Example 36

1-(4-Benzoyloxyphenyl)-4-formyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

0.83g of desired compound was obtained from 1-(4-benzoyloxyphenyl)-4-ethoxycarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole (1.46g) in the similar manner to that of Example 30 (63.3%).

25

IR (Neat, cm^{-1}) : 3217, 3126, 3059, 2947, 2831, 2760, 1687, 1606.

NMR (DMSO- d_6 , δ) : 3.84(3H, s), 5.16(2H, s), 6.82(1H, d, J=8.5Hz), 7.14(2H, dt, J=8.9Hz and 2.0Hz), 7.35-7.50(7H, m), 7.66(1H, dd, J=8.6Hz and 2.5Hz), 8.11(1H, d, 2.3Hz), 8.35(1H, s), 9.84(1H, s).

30

MS : 386 (M+H)⁺.

Example 37

1-(4-Benzoyloxyphenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

5

0.48g of desired compound was obtained from 1-(4-benzyloxyphenyl)-4-formyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 36 (0.83g) in the similar manner to that of Example 29-1 (54.7%).

10

IR (Neat, cm^{-1}) : 3429, 3209, 3151, 3064, 3028, 2979, 2949, 2875, 2549, 1734, 1604.

NMR ($\text{DMSO}-d_6$, δ) : 3.84(3H, s), 5.15(2H, s), 6.80(1H, d, $J=8.5\text{Hz}$), 7.00(1H, t, $J=54.8\text{Hz}$), 7.12(2H, d, $J=9.0\text{Hz}$), 7.27-7.49(7H, m), 7.63(1H, dd, $J=8.6\text{Hz}$ and 2.5Hz), 7.81(1H, t, $J=2.2\text{Hz}$), 8.07(1H, d, $J=1.8\text{Hz}$).

15

MS : 408 ($\text{M}+\text{H}$)⁺.

Example 38

4-Difluoromethyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

20

0.48g of desired compound was obtained from 1-(4-benzyloxyphenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 37 (0.48 g) in the similar manner to that of Example 32 (ca.100%).

25

MP : 155-156°C.

IR (KBr, cm^{-1}) : 3012, 2962, 2808, 2681, 2603, 1603.

NMR ($\text{DMSO}-d_6$, δ) : 3.83(3H, s), 6.77-6.86(3H, m), 6.99(1H, t, $J=54.9\text{Hz}$), 7.19(2H, d, $J=8.8\text{Hz}$), 7.63(1H, dd, $J=8.7\text{Hz}$ and 2.5Hz), 7.76(1H, t, $J=2.2\text{Hz}$), 8.06(1H, d, $J=2.4\text{Hz}$), 10.06(1H, br).

30

MS : 318 ($\text{M}+\text{H}$)⁺.

Example 39

4-Difluoromethyl-2-(2-methoxy-5-pyridinyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole

5 0.2g of desired compound was obtained from 4-difluoromethyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 38 (0.17g) in the similar manner to that of Example 33 (83.1%).

10 IR (Neat, cm^{-1}) : 3429, 3224, 3165, 3084, 3020, 2958, 2860, 1724, 1664, 1604.

NMR ($\text{DMSO}-d_6$, δ) : 3.84(3H, s), 6.80(2H, d, $J=8.4\text{Hz}$), 7.03(1H, t, $J=54.8\text{Hz}$), 7.56-7.71(4H, m), 7.99(1H, t, $J=2.2\text{Hz}$), 8.09(1H, d, $J=2.4\text{Hz}$).
MS : 450 ($\text{M}+\text{H}$)⁺.

15 Example 40

1-(4-Cyanophenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

20 62mg of desired compound was obtained from 4-difluoromethyl-2-(2-methoxy-5-pyridinyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole obtained by Example 39 (0.2g) in the similar manner to that of Example 34 (42.7%).

MP : 160-161°C.

25 IR (KBr, cm^{-1}) : 3219, 3140, 3101, 3051, 3005, 2985, 2954, 2241, 1608.
NMR ($\text{DMSO}-d_6$, δ) : 3.85(3H, s), 6.82(1H, d, $J=8.6\text{Hz}$), 7.04(1H, t, $J=54.7\text{Hz}$), 7.57-7.63(3H, m), 7.99-8.03(3H, m), 8.11(1H, d, $J=2.3\text{Hz}$).
MS : 327 ($\text{M}+\text{H}$)⁺.

30 Example 41-1

4-Ethoxycarbonyl-4,5-dihydro-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

5.41g of desired compound was obtained from a mixture of
N¹-(4-methoxyphenyl)-2-methoxy-5-amidinopyridine (5g) and ethyl
2-chloroacrylate (3.92g) in the similar manner to that of Example 12-1
(78.3%).

IR (Neat, cm⁻¹) : 3448, 3429, 3411, 3381, 3047, 2981, 2951, 2904, 2841,
1736, 1608.

NMR (DMSO-d₆, δ) : 1.24(3H, t, J=7.1 Hz), 3.73(3H, s), 3.83(3H, s),
4.05(2H, d, J=9.5Hz), 4.17(2H, q, J=7.1Hz), 4.81(1H, t, J=9.5Hz),
6.77(1H, d, J=8.5Hz), 6.79-6.96(4H, m), 7.67(1H, dd, J=8.6Hz and 2.4Hz),
8.17(1H, d, J=2.3Hz).

MS : 356 (M+H)⁺.

Example 41-2

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-
imidazole

3.71g of desired compound was obtained from a suspension of
4-ethoxycarbonyl-4,5-dihydro-1-(4-methoxyphenyl)-2-(2-methoxy-5-py-
ridinyl)-1H-imidazole obtained by Example 41-1 (5.41g) in
N,N-dimethylformamide (54ml) in the similar manner to that of Example
25-2 (69%).

MP : 135-137 °C.

IR (KBr, cm⁻¹) : 3413, 3224, 3145, 3070, 2949, 2902, 2837, 1703, 1610.

NMR (DMSO-d₆, δ) : 1.29(3H, t, J=7.1Hz), 3.81(3H, s), 3.83(3H, s),
4.28(2H, q, J=7.1Hz), 6.80(1H, d, J=8.6Hz), 7.04(2H, dt, J=8.9Hz and
2.0Hz), 7.34(2H, dt, J=8.9Hz and 2.2Hz), 7.64(1H, dd, J=8.6Hz and 2.5Hz),
8.06(1H, d, J=2.4Hz), 8.11(1H, s).

MS : 354 (M+H)⁺.

Example 42

4-Formyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

5 0.88g of desired compound was obtained from 4-ethoxycarbonyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 41-2 (1.7g) in the similar manner to that of Example 30 (59.1%).

IR (Neat, cm^{-1}) : 3435, 3367, 3134, 3074, 3006, 2960, 2846, 1682, 1608.

10 NMR ($\text{DMSO}-d_6$, δ) : 3.81(3H, s), 3.84(3H, s), 6.82(1H, d, $J=8.5\text{Hz}$), 7.06(2H, dt, $J=8.9\text{Hz}$ and 1.9Hz), 7.37(2H, dt, $J=8.9\text{Hz}$ and 1.9Hz), 7.65(1H, dd, $J=8.6\text{Hz}$ and 2.5Hz), 8.11(1H, d, $J=2.1\text{Hz}$), 8.34(1H, s), 9.84(1H, s).

MS : 310 ($\text{M}+\text{H}$) $^+$.

15

Example 43

4-Difluoromethyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

20 332mg of desired compound was obtained from 4-formyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 42 (0.83g) in the similar manner to that of Example 31 (36.5%).

MP : 106-107 $^{\circ}\text{C}$.

25 IR (KBr, cm^{-1}) : 3398, 3153, 3114, 2997, 2947, 2844, 1606.

NMR ($\text{DMSO}-d_6$, δ) : 3.81(3H, s), 3.83(3H, s), 6.80(1H, d, $J=8.8\text{Hz}$), 7.00(1H, t, $J=54.9\text{Hz}$), 7.04(2H, dt, $J=8.9\text{Hz}$ and 2.1Hz), 7.33(2H, dt, $J=8.8\text{Hz}$ and 2.1Hz), 7.63(1H, dd, $J=8.6\text{Hz}$ and 2.5Hz), 7.80(1H, t, $J=2.3\text{Hz}$), 8.07(1H, d, $J=2.4\text{Hz}$).

30 MS : 332 ($\text{M}+\text{H}$) $^+$.

Example 44

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

1.5g of desired compound was obtained from a suspension of
5 N¹-(4-methoxyphenyl)-2-methoxy-5-amidinopyridine (1.5g) in
2-propanol (10ml) in the similar manner to that of Example 9 (72.8%).

Example 45

1-(4-Benzyloxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-imidazole

10

To a solution of 4-ethoxycarbonyl-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 29-2 (1.46g) in ethanol (10ml) and tetrahydrofuran (10ml), 1N aqueous sodium hydroxide (6.81ml) was added.

15

After stirring at room temperature overnight, the reaction mixture was poured into water and ethyl acetate, and extracted with water. Then, the water layer was acidified with 1N hydrochloric acid, extracted with ethyl acetate, dried over magnesium sulfate, and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with
20 diisopropyl ether to give the target compound (1.1g).

MP : 113-115°C.

¹H NMR (200MHz, DMSO-d₆, δ) : 3.75(3H, s), 5.15(2H, s), 6.88(2H, d, J=8.8Hz), 7.10(2H, d, J=8.9Hz), 7.24-7.45(9H, m), 7.96(1H, s),

25

11.0-12.5(1H, br).

IR (KBr, cm⁻¹) : 3392, 3224, 3145, 3076, 2972, 2935, 2893, 1701, 1610.

Example 46

1-(4-Benzyloxyphenyl)-4-(N-ethyl-N-methylcarbamoyl)-2-(4-methoxyphenyl)-1H-imidazole

30

A mixture of 1-(4-benzyloxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-

imidazole obtained by Example 45 (0.44g). ethylmethylaniline (118ml), 1-hydroxybenzotriazole (186mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (263mg) in N,N-dimethylformamide (5ml) was stirred at room temperature overnight.

5 The reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=1:1). The resulting precipitates were corrected by filtration and washed with diisopropyl ether to give the
10 target compound (0.44g).

MP : 118-119°C.

¹H NMR (DMSO-d₆, δ) : 1.06-1.28(3H, m), 2.91-3.02(2H, m), 3.40-3.54(2H, m), 3.74(3H, s), 3.93-4.07(1H, m), 5.15(2H, s), 6.88(2H, d, J=8.8Hz),
15 7.10(2H, d, J=8.9Hz), 7.24-7.30(4H, m), 7.36-7.49(5H, m), 7.73(1H, s).

IR (KBr, cm⁻¹): 3124, 3066, 2958, 2935, 2839, 1608.

Mass m/e : 442 (M⁺+1).

Example 47

20 4-(N-Ethyl-N-methylcarbamoyl)-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

The target compound was obtained from 1-(4-benzyloxyphenyl)-4-(N-ethyl-N-methylcarbamoyl)-2-(4-methoxyphenyl)-1H-imidazole obtained
25 by Example 46 in the similar manner to that of Example 62 described later.

¹H NMR (DMSO-d₆, δ) : 1.10-1.28(3H, m), 2.90-3.02(2H, m), 3.40-3.50(2H, m), 3.74(3H, s), 3.91-4.03(1H, m), 6.82(2H, d, J=8.7Hz), 6.88(2H, d, J=8.9Hz),
30 7.11(1H, s), 7.14(2H, d, J=8.7Hz), 7.27(2H, d, J=8.7Hz), 7.67(1H, s).

IR (KBr, cm⁻¹) : 3126, 3091, 3018, 2968, 2933, 2831, 2738, 2677, 2600.

2476, 1612.

MS m/e : 352 ($M^+ + 1$).

Example 48

5 1-(4-Benzoyloxyphenyl)-4-(N,N-diethylcarbamoyl)-2-(4-methoxyphenyl)
-1H-imidazole

The target compound was obtained from 1-(4-benzyloxyphenyl)-4-
carboxy-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 45 and
10 N,N-diethylamine in the similar manner to that of Example 46.

MP : 146-147°C.

1H NMR (DMSO- d_6 , δ) : 1.10-1.30(6H, m), 3.38-3.50(2H, m), 3.74(3H,
s), 3.85-4.02(2H, m), 5.15(2H, s), 6.88(2H, d, $J=8.8\text{Hz}$), 7.10(2H, d,
15 $J=8.9\text{Hz}$), 7.24-7.30(4H, m), 7.36-7.49(5H, m), 7.72(1H, s).

IR (KBr, cm^{-1}) : 3113, 2972, 2929, 1593.

MS m/e : 456 ($M^+ + 1$).

Example 49

20 4-(N,N-Diethylcarbamoyl)-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1
H-imidazole

The target compound was obtained from 1-(4-benzyloxyphenyl)-4-
(N,N-diethylcarbamoyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by
25 Example 48 in the similar manner to that of Example 62 described later.

1H NMR (DMSO- d_6 , δ) : 1.02-1.30(6H, m), 3.22-3.48(2H, m), 3.73(3H,
s), 3.83-4.02(2H, m), 6.81-6.92(4H, m), 7.14(2H, dd, $J=6.7\text{Hz}$, 2.0Hz),
7.27(2H, dt, $J=9.4\text{Hz}$, 2.5Hz), 7.66(1H, s).

30 IR (KBr, cm^{-1}) : 3145, 3030, 2970, 2937, 2833, 1693, 1606.

MS m/e : 366 ($M^+ + 1$).

Example 50

1-(4-Benzoyloxyphenyl)-2-(4-methoxyphenyl)-4-(1-piperidinecarbonyl)-1H-imidazole

5 The target compound (0.5g) was obtained from 1-(4-benzyloxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 45 and piperidine in the similar manner to that of Example 46.

10 ¹H NMR (200MHz, DMSO-d₆, δ) : 1.507-1.572(4H, m), 1.605-1.67(2H, m), 3.462-3.644(2H, m), 3.74(3H, s), 3.918-4.244(2H, m), 5.144(2H, s), 6.879(2H, d, J=4.5Hz), 7.096(2H, d, J=4.5Hz), 7.251(2H, d, J=4.3Hz), 7.278(2H, d, J=4.3Hz), 7.348-7.478(5H, m), 7.721(1H, s).

IR (KBr, cm⁻¹) : 3116, 3033, 2931, 2850.

MS m/e : 468 (M+H)⁺.

15

Example 51

1-(4-Hydroxyphenyl)-2-(4-methoxyphenyl)-4-(1-piperidinecarbonyl)-1H-imidazole

20 The target compound (0.41g) was obtained from 1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4-(1-piperidinecarbonyl)-1H-imidazole obtained by Example 50 in the similar manner to that of Example 62 described later.

25 ¹H NMR (200MHz, DMSO-d₆, δ) : 1.509-1.577(4H, m), 1.611-1.674(2H, m), 3.51-3.657(2H, m), 3.734(3H, s), 4.035-4.224(2H, m), 6.814(2H, d, J=4.4Hz), 6.881(2H, d, J=4.3Hz), 7.136(2H, d, J=4.4Hz), 7.256(2H, d, J=4.4Hz), 7.668(1H, s), 9.908(1H, bs).

IR (KBr, cm⁻¹) : 3151, 3035, 2935, 2852, 1606.

30 MS m/e : 378 (M+H)⁺.

Example 52-1

N¹-(4-Benzoyloxyphenyl)-4-methoxybenzamidine

To a solution of 4-benzoyloxyaniline hydrochloride (3g) in tetrahydrofuran (15ml), 1.0M sodium bis(trimethylsilyl)amide in tetrahydrofuran (26.7ml) was added dropwise at room temperature. After the mixture was stirred for 20min, anisonitrile (1.69g) was added.

The reaction mixture was stirred for 4hrs, and then poured into 300ml of ice-water. The precipitate was collected by filtration, washed with diisopropyl ether to give the target compound (3.3g).

¹H NMR (200MHz, DMSO-d₆, δ) : 3.8(3H, s), 5.05(2H, s), 6.09(2H, bs), 6.74-6.8(2H, m), 6.96(4H, d, J=8.5Hz), 7.29-7.49(5H, m), 7.92(2H, d, J=8.9Hz).

MS m/e : 333 (M+H)⁺.

Example 52-2

4-Cyano-4,5-dihydro-1-(4-benzoyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of N¹-(4-Benzoyloxyphenyl)-4-methoxybenzamidine obtained by Example 52-1 (2g), 2-chlorocyanoethylene (0.36ml) and N,N-diisopropylethylamine (0.79ml) in tetrahydrofuran (10ml) was stirred at reflux condition overnight.

After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=1:1) to give the target compound (0.82g).

MP : 121-122°C.

¹H NMR (200MHz, DMSO-d₆, δ) : 3.74(3H, s), 4.11-4.19(2H, m), 5.03(2H,

s), 5.16-5.25(1H, m). 6.87(2H, d, J=9Hz), 6.93(4H, s), 7.29-7.44(7H, m).

MS (ESI⁺) m/e : 384 (M+H)⁺.

5 Example 52-3

4-Cyano-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

10 A suspension of 4-cyano-4,5-dihydro-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 52-2 (0.8g) and manganese(IV) oxide (0.91g) in N,N-dimethylformamide (8ml) was stirred at 100°C for 4hrs.

15 After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. To the solution of the residue in N,N-dimethylformamide (8ml), phosphorus oxychloride (0.58ml) was added under stirring at 0°C.

20 After stirring at room temperature for 2hrs, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=3:1 to 1:1) to give the target compound (0.74g) as an oil.

25 ¹H NMR (200MHz, DMSO-d₆, δ) : 3.75(3H, s), 5.16(2H, s), 6.89(2H, d, J=8.5Hz), 7.12(2H, d, J=9Hz), 7.25-7.48(9H, m), 8.4(1H, s).

MS (ESI⁺) m/e : 382 (M+H)⁺.

Example 53

4-Cyano-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

30

The target compound was obtained from 4-cyano-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by

Example 52-3 in the similar manner to that of Example 62 described later.

¹H NMR (CDCl₃, δ) : 3.74(3H, s), 6.75-6.95(4H, m), 7.10-7.35(4H, m),
8.36(1H, s), 9.98(1H, bs).

5 MS (ESI, m/e) : 292 (M+1).

Example 54-1

1-(4-Benzyloxyphenyl)-4-cyano-4,5-dihydro-2-(2-methoxy-5-pyridinyl)
)-1H-imidazole

10

The target compound was obtained from N¹-(4-Benzyloxyphenyl)-2-methoxy-5-pyridinyl amidine in the similar manner to that of Example 52-2.

15 ¹H NMR (200MHz, DMSO-d₆, δ) : 3.84(3H, s), 4.15-4.21(2H, m), 5.05(2H, s), 5.25(1H, dd, J=8.8, 10.5Hz), 6.78(1H, d, J=8.5Hz), 6.92-7.04(4H, m), 7.32-7.45(5H, m), 7.66(1H, dd, J=2.5, 8.5Hz), 8.19(1H, d, J=2Hz).
MS (ESI⁺) m/e : 385 (M+H)⁺.

20 Example 54-2

1-(4-Benzyloxyphenyl)-4-cyano-2-(2-methoxy-5-pyridinyl)-1H-imidazole

25 The target compound was obtained from 1-(4-Benzyloxyphenyl)-4-cyano-4,5-dihydro-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 54-1 in the similar manner to that of Example 52-3.

30 ¹H NMR (200MHz, DMSO-d₆, δ) : 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, J=8Hz), 7.14(2H, d, J=9Hz), 7.316-7.5(7H, m), 7.63(1H, dd, J=2.3, 8.5Hz), 8.1(1H, dd, J=2.5Hz), 8.47(1H, s).
MS (ESI⁺) m/e : 383 (M+H)⁺.

Example 55

1-(4-Benzyloxyphenyl)-4-ethylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

5 To a solution of 1-(4-benzyloxyphenyl)-4-cyano-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 54-2 (1.1g) in tetrahydrofuran (10ml), 1N solution of ethylmagnesium bromide in tetrahydrofuran (8.63ml) was added under stirring at 0°C.

10 After stirring at room temperature for 1hr, the reaction mixture was poured into aqueous 10% potassium hydrogen sulfate and stirred at room temperature for 30min. The mixture was alkalized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate, washed with water, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with
15 diisopropyl ether to give the target compound (1.07g).

MP : 126-128°C.

¹H NMR (DMSO-d₆, δ) : 1.10(3H, t, J=7.4Hz), 2.95(2H, q, J=7.4Hz), 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, J=8.6Hz), 7.12(2H, d, J=8.9Hz),
20 7.32-7.49(7H, m), 7.66(1H, dd, J=8.6Hz, 2.4Hz), 8.08(1H, d, J=2.4Hz), 8.17(1H, s).

IR (KBr, cm⁻¹) : 3217, 3126, 3066, 3030, 2972, 2939, 2883, 1666, 1610.

MS m/e : 414 (M⁺+1).

25 Example 56

4-Ethylcarbonyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

30 The target compound was obtained from 1-(4-benzyloxyphenyl)-4-ethylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 55 in the similar manner to that of Example 62 described later.

MP : 221-223°C.

¹H NMR (DMSO-d₆, δ) : 1.10 (3H, t, J=7.3Hz), 2.95 (2H, q, J=7.3Hz), 3.84 (3H, s), 6.79-6.88 (3H, m), 7.20 (2H, dt, J=9.6Hz, 2.7Hz), 7.66 (1H, dd, J=8.7Hz, 2.4Hz), 8.07 (1H, d, J=2.4Hz), 9.97 (1H, s).

5 IR (KBr, cm⁻¹) : 3215, 3136, 3053, 2978, 2947, 2900, 1676, 1603.

MS m/e : 324 (M⁺+1).

Example 57

10 1-(4-Benzylloxyphenyl)-4-isopropylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

The target compound (1.04g) was obtained from 1-(4-benzylloxyphenyl)-4-cyano-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 54-2 in the similar manner to that of Example 15 55.

MP : 118-120°C.

¹H NMR (DMSO-d₆, δ) : 1.14 (6H, d, J=6.8Hz), 3.56-3.70 (1H, m), 3.84 (3H, s), 5.16 (2H, s), 6.81 (1H, d, J=8.5Hz), 7.13 (2H, dd, J=9.1Hz, 2.3Hz), 20 7.32-7.49 (7H, m), 7.67 (1H, dd, J=8.5Hz, 2.4Hz), 8.08 (1H, d, J=2.4Hz), 8.19 (1H, s).

IR (KBr, cm⁻¹) : 3126, 3064, 3033, 2968, 2875, 1660, 1608.

MS m/e : 428 (M⁺+1).

25 Example 58

4-Isopropylcarbonyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

The target compound was obtained from 1-(4-benzylloxyphenyl)-4-isopropylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 57 in the similar manner to that of Example 62 described later. 30

MP : 185-187°C.

¹H NMR (DMSO-*d*₆, δ) : 1.14(6H, d, J=6.8Hz), 3.56-3.69(1H, m), 3.84(3H, s), 6.79-6.86(3H, m), 7.17-7.25(2H, m), 7.67(1H, dd, J=8.8Hz, 2.4Hz),
5 8.07(1H, d, J=2.4Hz), 8.14(1H, s), 9.98(1H, s).

IR (KBr, cm⁻¹) : 3134, 2972, 2891, 2812, 2744, 2681, 2607, 1676, 1612.

MS m/e : 338 (M⁺+1).

Example 59

10 1-(4-Benzyloxyphenyl)-4-cyclopentylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

To a solution of 1-(4-benzyloxyphenyl)-4-cyano-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 54-2 (0.8g) in
15 tetrahydrofuran (8ml), 2N solution of cyclopentylmagnesium chloride in tetrahydrofuran (3.14ml) was added under stirring at 0°C.

After stirring at room temperature for 2hrs, the reaction mixture was poured into aqueous 10% potassium hydrogen sulfate and stirred at room temperature for 30min. The mixture was alkalized with saturated
20 aqueous sodium hydrogen carbonate and extracted with ethyl acetate, washed with water, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with diisopropyl ether to give the target compound (0.82g).

25 ¹H NMR (200MHz, DMSO-*d*₆, δ) : 1.57-1.949(m, 8H), 3.764(1H, t, J=7.9Hz), 3.84(3H, s), 5.156(2H, s), 6.81(1H, d, J=8.5Hz), 7.12(2H, d, J=9Hz), 7.328-7.501(7H, m), 7.669(1H, dd, J=8.5Hz, 2.5Hz), 8.078(1H, d, J=1Hz), 8.188(1H, s).

IR (KBr, cm⁻¹) : 3122, 2947, 2868, 1658, 1608.

30 MS (ESI⁺, m/e) : 454 (M+H).

Example 60

4-Cyclopentylcarbonyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

The target compound was obtained from 1-(4-Benzyloxyphenyl)-4-cyclopentylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 59 in the similar manner to that of Example 62 described later.

¹H NMR (200MHz, DMSO-d₆, δ) : 1.577-1.968(8H, m), 3.761(1H, t, J=8Hz), 3.836(3H, s), 6.793-6.859(3H, m), 7.21(2H, d, J=7Hz), 7.667(1H, dd, J=9Hz, 2.5Hz), 8.069(1H, d, J=1.5Hz), 8.143(1H, s).

IR (KBr, cm⁻¹) : 3220, 3124, 2960, 1674, 1608.

MS (ESI⁺, m/e) : 364 (M+H).

Example 61

1-(4-Benzyloxyphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

A mixture of N¹-(4-Benzyloxyphenyl)-4-methoxybenzamidinium (1g), 3-bromo-1,1,1-trifluoropropanone (0.47ml) and sodium hydrogencarbonate (506mg) in isopropyl alcohol (10ml) was stirred at reflux condition overnight.

After cooling to room temperature, the reaction mixture was filtrated and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=1:1) to give the target compound (0.55g) as an oil.

¹H NMR (DMSO-d₆, δ) : 3.75(3H, s), 5.16(2H, s), 6.86-6.92(2H, m), 7.09-7.13(2H, m), 7.25-7.50(9H, m), 8.08(1H, d, J=1.4Hz).

IR (Neat, cm⁻¹) : 3120, 3068, 2973, 2843, 1610.

MS m/e : 425 ($M^+ + 1$).

Example 62

1-(4-Hydroxyphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

1-(4-Benzoyloxyphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole obtained by Example 61 (0.55g) and dry 20% Pd(OH)₂/C (200mg) in ethanol (10ml) and cyclohexene (5ml) was stirred at reflux condition for 2hrs and cooled to room temperature.

After filtration, the reaction mixture was evaporated in vacuo to give the target compound (0.44g).

MP : 215-216°C.

¹H NMR (DMSO-d₆, δ) : 3.74(3H, s), 6.81-6.92(4H, m), 7.16-7.30(4H, m), 8.03(1H, d, J=1.3Hz).

IR (KBr, cm⁻¹) : 3149, 3103, 3037, 2964, 2910, 2829, 2690, 2611, 1649, 1614.

MS m/e : 335 ($M^+ + 1$).

[A] ANALGESIC ACTIVITY :

Effect on adjuvant arthritis in rats :

(i) Test Method :

Analgesic activity of a single dose of agents in arthritic rats was studied.

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50 μ l of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind paws and body weight on day 22.

Drugs (Test compounds) were administered and the pain threshold was measured 2hrs after drug administration. The intensity of

to obtain serum. A 100 μ l aliquot of serum was mixed with 400 μ l methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4°C and was assayed for TXB₂ using an enzyme immunoassay kit according to the manufacturer's procedure.

5 For a test compound, the results were expressed as percent inhibition of thromboxane B₂ (TXB₂) production relative to control incubations containing dimethyl sulfoxide vehicle.

The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC₅₀ value was calculated by least squares method.

10

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

15

500 μ l aliquots of human whole blood were incubated with either 2 μ l dimethyl sulfoxide vehicle or 2 μ l of a test compound at final concentrations for 15 min at 37°C. This was followed by incubation of the blood with 10 μ l of 5mg/ml lipopolysaccharide for 24hrs at 37°C for induction of COX-II. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000 x g for 5 min at 4 °C to obtain plasma. A 100 μ l aliquot of plasma was mixed with 400 μ l methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4°C and was assayed for prostaglandin E₂ (PGE₂) using a radioimmunoassay kit after conversion of PGE₂ to its methyl oximate derivative according to the manufacturer's procedure.

20

25

For a test compound, the results were expressed as percent inhibition of PGE₂ production relative to control incubations containing dimethyl sulfoxide vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple

30

linear regression. IC₅₀ value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μ M)	COX-II IC50 (μ M)
1-2	< 0.01	\approx 0.1
3-2	< 0.01	\approx 0.1
4-2	< 0.01	\approx 0.1
8	< 0.01	\approx 0.1
11	< 0.01	\approx 0.1
17	< 0.01	\approx 0.1
20	< 0.01	\approx 0.1
21	< 0.01	\approx 0.1
24	< 0.01	\approx 0.1
34	< 0.01	\approx 0.1
40	< 0.01	\approx 0.1
43	< 0.01	\approx 0.1

5 It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

10 Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc. So compound (I) or a salt thereof is expected to be useful as medicament.

15 The object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

20 The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen

diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.], inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.], inflammatory eye condition [e.g. conjunctivitis, etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varioliforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.], gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodosa, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimer's disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

And compound (I) or a salt thereof is expected to be useful as analgesic agent, which is usable for treating or preventing pains caused by or associated with acute or chronic inflammations, for example rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid

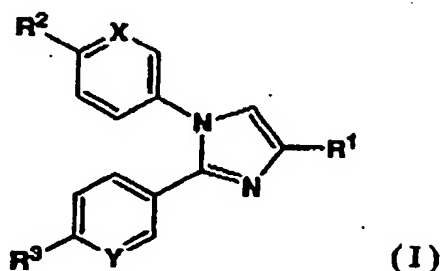
spondylitis, gouty arthritis, juvenile arthritis; lumbago;
cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and
tumescence after operation or injury.

5 Although the present invention has been fully described by way
of example, it is to be understood that various changes and modifications
will be apparent to those skilled in the art. Therefore, unless
otherwise such changes and modifications depart from the scope of the
present invention hereinafter defined, they should be construed as being
10 included therein.

Throughout this specification and the claims which follow, unless the context requires
otherwise, the word "comprise", and variations such as "comprises" and "comprising", will
be understood to imply the inclusion of a stated integer or step or group of integers or steps
but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I):



[wherein

R¹ is (lower)alkyl, halogen-substituted (lower)alkyl,
hydroxy-substituted (lower)alkyl, cycloalkyl, carbamoyl,
N-[(lower)alkyl]carbamoyl, N,N-di[(lower)alkyl]carbamoyl,
formyl, (lower)alkanoyl, carboxy, [(lower)alkoxy]carbonyl,
cyano, cycloalkylcarbonyl or heterocycliccarbonyl;

R² is halogen, cyano, hydroxy, (lower)alkoxy,
aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl,
carbamoyl, formyloxy, (lower)alkanoyloxy,
[(lower)alkyl]sulfonyloxy, [halogen-substituted
(lower)alkyl]sulfonyloxy or carboxy;

R³ is (lower)alkoxy, hydroxy, amino, [(lower)alkyl]amino, or
di[(lower)alkyl]amino;

X and Y are each CH or N]
or pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1,

wherein

R¹ is (lower)alkyl, halogen-substituted (lower)alkyl, cycloalkyl,
N,N-di[(lower)alkyl]carbamoyl, (lower)alkanoyl, or cyano;

R² is halogen, cyano, hydroxy, or lower alkoxy;

R³ is lower alkoxy;

X and Y are each CH, X is N and Y is CH, or X is CH and Y is N;
or pharmaceutically acceptable salts thereof.

5 3. A medicament comprising a compound of Claim 1 or 2 as an active ingredient.

10 4. A pharmaceutical composition comprising a compound of Claim 1 or 2 as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient.

15 5. A method for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegenerative diseases which comprises administering an effective amount of the compound of Claim 1 or 2 to human beings or animals.

20 6. The compound of Claim 1 or 2 for use in the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegenerative diseases in human beings or animals.

25 7. Use of the compound of Claim 1 or 2 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegenerative diseases in human beings or animals.

30 8. The analgesic agent comprising the compound of Claim 1 or 2, which is usable for treating and/or preventing pains caused by or associated with acute or chronic inflammations.

9. The analgesic agent of Claim 8, which is usable for treating or

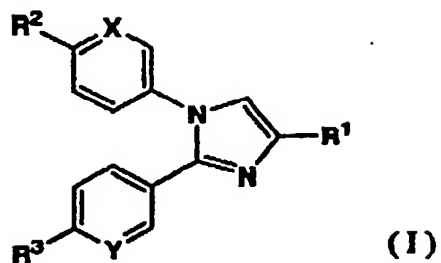
preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthrititis; pain and tumescence after operation or injury.

10. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in Claim 1 or 2 and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegenerative diseases.

DATED this 24th day of July 2003
Fujisawa Pharmaceutical Co., Ltd
by DAVIES COLLISON CAVE
Patent Attorneys for the applicant

A B S T R A C T

A compound of the formula (I):



5

wherein

R¹ is cyano, etc;

R² is hydroxy, etc;;

10 R³ is (lower)alkoxy, etc;;

X and Y are each CH or N;

or pharmaceutically acceptable salts thereof, which are useful as a
medicament.

This Page is inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLORED OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REPERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
problems checked, please do not report the
problems to the IFW Image Problem Mailbox**